

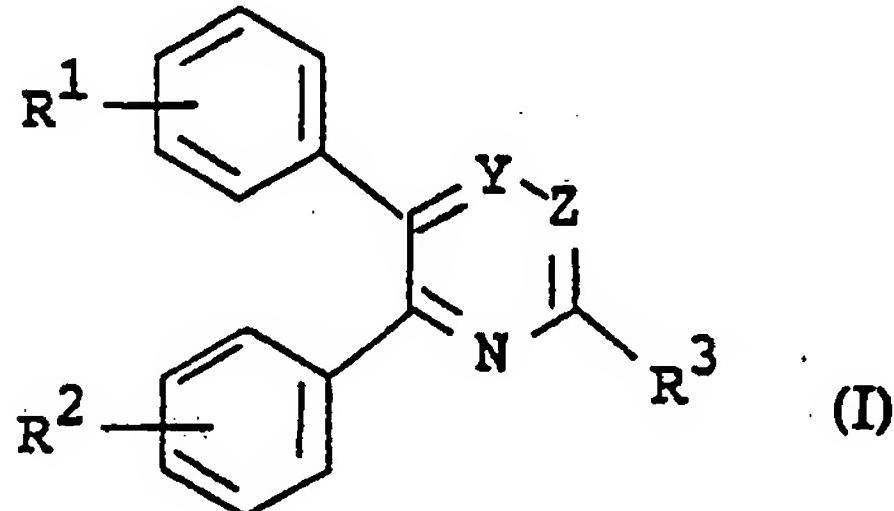


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(54) Title: HETEROCYCLIC COMPOUNDS



(57) Abstract

Heterocyclic compounds of formula (I), wherein R¹ and R² are each lower alkoxy, R³ is substituted amino, etc., Y is CH or N and Z is CH or N, and pharmaceutically acceptable salts thereof which are useful as a medicament.

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DESCRIPTION

HETEROCYCLIC COMPOUNDS

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TECHNICAL FIELD

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

10

BACKGROUND ART

Some heterocyclic compounds have been known as described, for example, in U.S. Patent 3,979,516, U.S. Patent 4,021,553, U.S. Patent 4,190,725 and U.S. Patent 4,318,911.

15

DISCLOSURE OF INVENTION

This invention relates to new heterocyclic compounds. More particularly, this invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

20

Accordingly, one object of this invention is to provide the new and useful heterocyclic compounds and pharmaceutically acceptable salts thereof which possess antithrombotic, vasodilating, and anti-inflammatory activities.

25

Another object of this invention is to provide processes for preparation of the heterocyclic compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said heterocyclic compounds or a pharmaceutically acceptable salt thereof.

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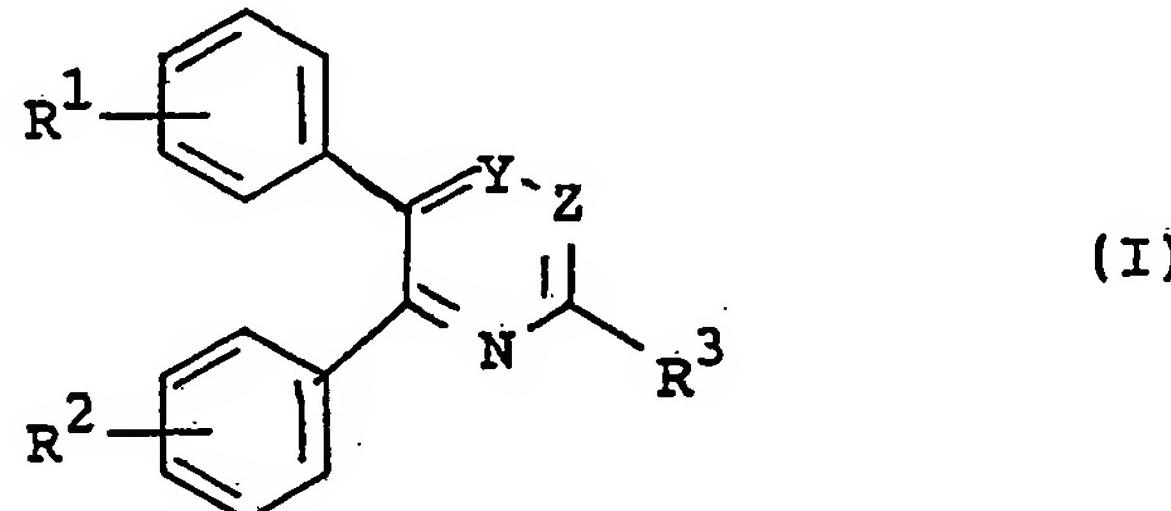
Still further object of this invention is to provide

- 2 -

a use of said heterocyclic compound or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of thrombosis, hypertension, cardiovascular or cerebrovascular diseases and inflammation, particularly thrombosis, in human being and animals.

The object heterocyclic compounds of the present invention are novel and can be represented by the following general formula (I) :

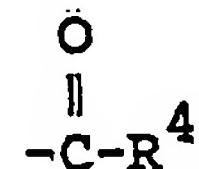
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wherein R¹ and R² are each lower alkoxy, R³ is heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have suitable substituent(s); substituted amino; carboxy(lower)alkenyl; carboxy(lower)alkyl; hydroxy(lower)alkyl; amino(lower)alkyl which may have suitable substituent(s); a group of the formula :

25



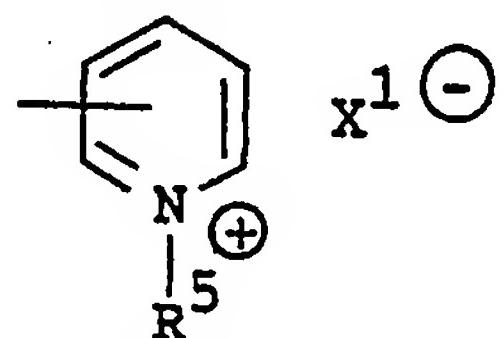
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- 3 -

(in which R⁴ is hydrogen, ethoxy,
mono(or di)lower alkylamino,
di(lower)alkylamino-(lower)-
alkylamino, heterocyclicamino
which may have suitable
substituent(s), or
heterocyclic group which may
have suitable substituent(s));
or a group of the formula :

10



15

(in which R⁵ is lower alkyl or
ar(lower)alkyl
which may have suitable
substituent(s), and
X¹ is an acid residue),

20

Y is CH or N and

Z is CH or N,

with proviso that

25

when R³ is pyridyl; piperidyl which may have hydroxy
group; piperazinyl which has lower alkyl group
or hydroxy(lower)alkyl group; morpholinyl; lower
alkenylamino; hydroxy(lower)alkylamino;
phenylamino which may have lower alkoxy group or
halogen on the benzene ring;

30

halophenyl(lower)alkylamino; phenylsulfonylamino
which has nitro group, amino group or halogen on the
benzene ring; or
amino substituted with two substituents selected
from the group consisting of lower alkyl and
hydroxy(lower)alkyl, and

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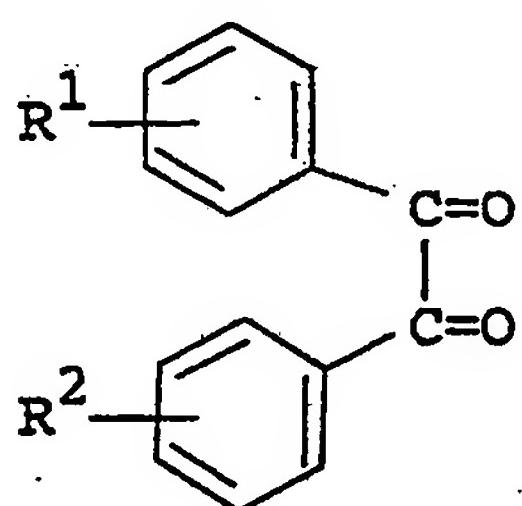
- 4 -

Y is N,
then Z is CH.

5 The object compound (I) of the present invention can
be prepared by the following processes.

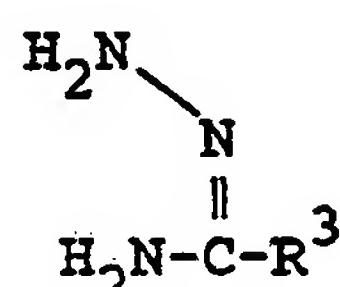
Process (1)

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(II)

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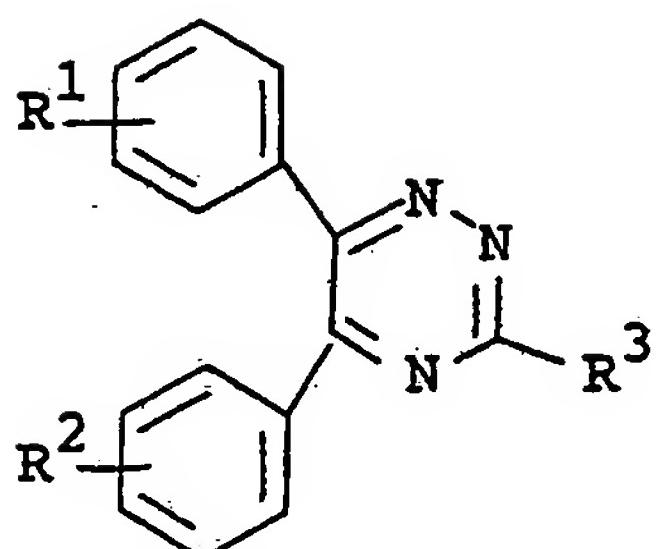


(III)

20

or a salt thereof

25



(Ia)

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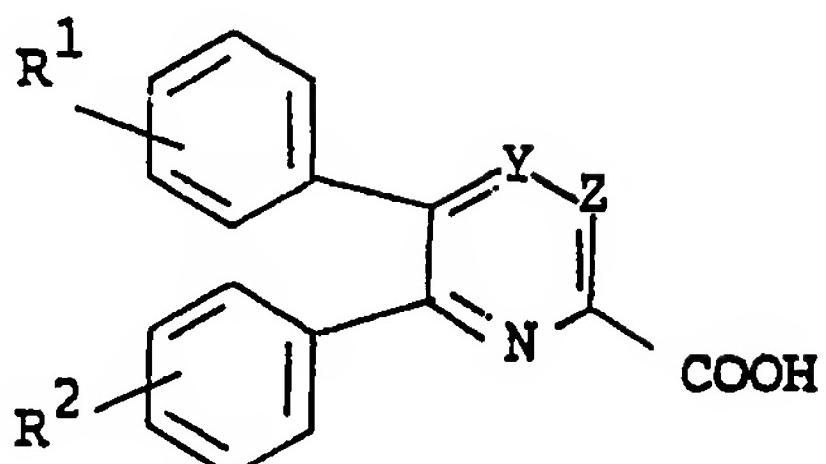
or a salt thereof

35

- 5 -

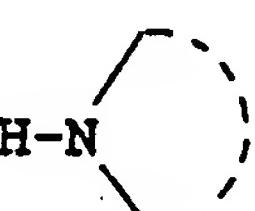
Process (2)

5



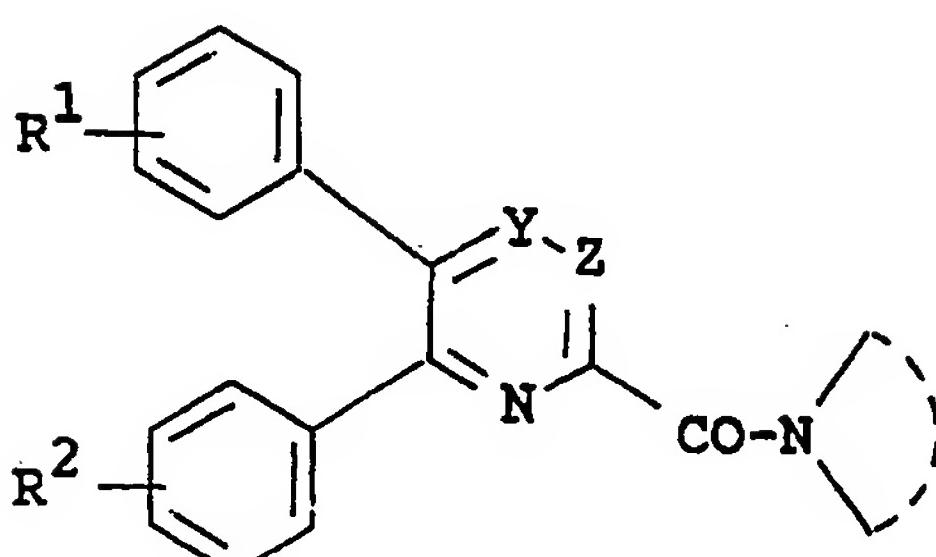
or its reactive derivative
at the carboxy group or
a salt thereof

10



or a salt thereof

15

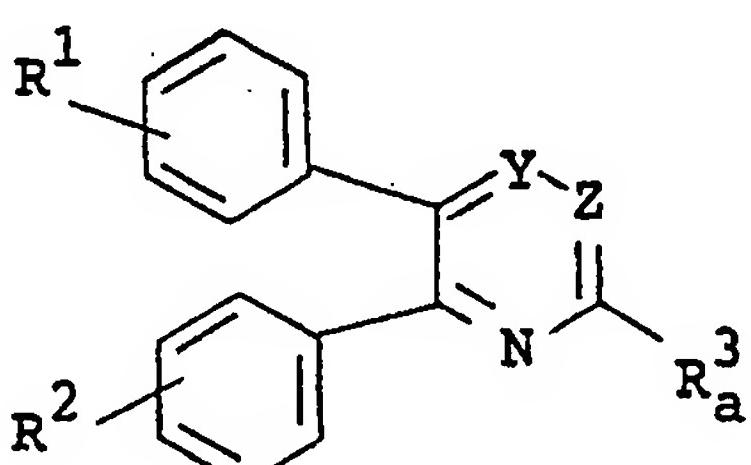


or a salt thereof

20

Process (3)

25



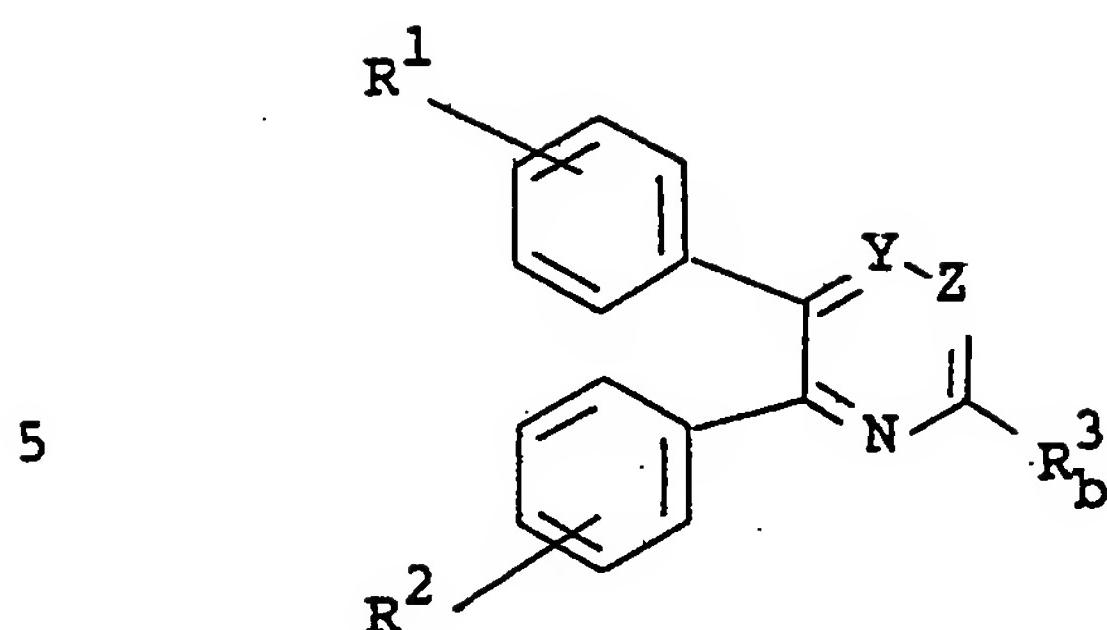
or a salt thereof

30

elimination reaction of
the amino-protective group

35

- 6 -



(Id)

or a salt thereof

Process (4)

10

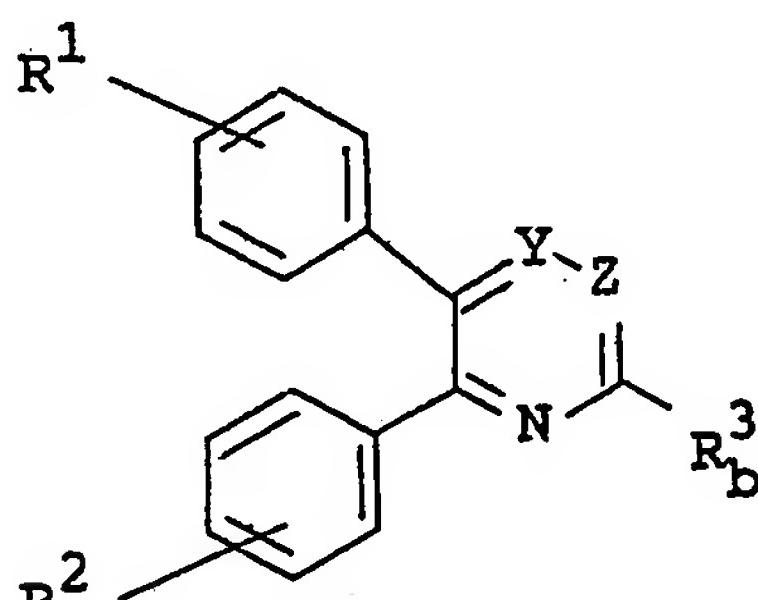
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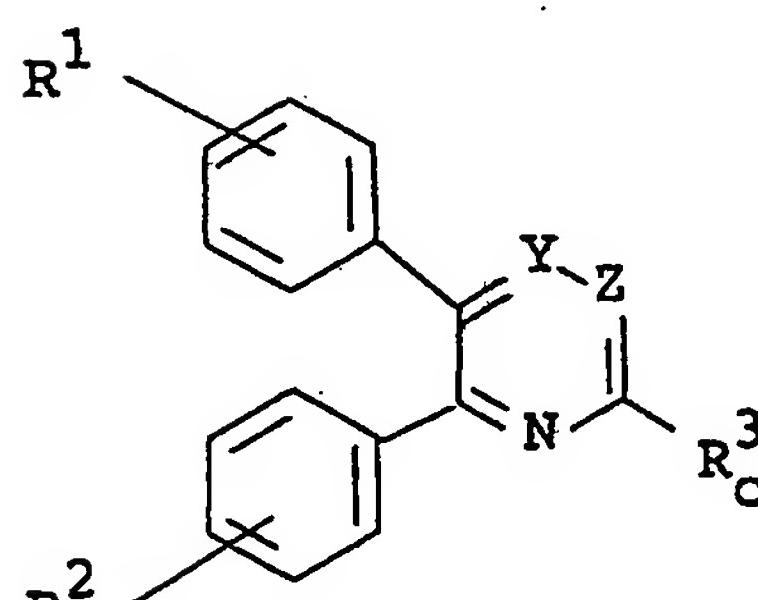
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(Id)

or its reactive derivative
at the amino group , or
a salt thereof

↓ acylation

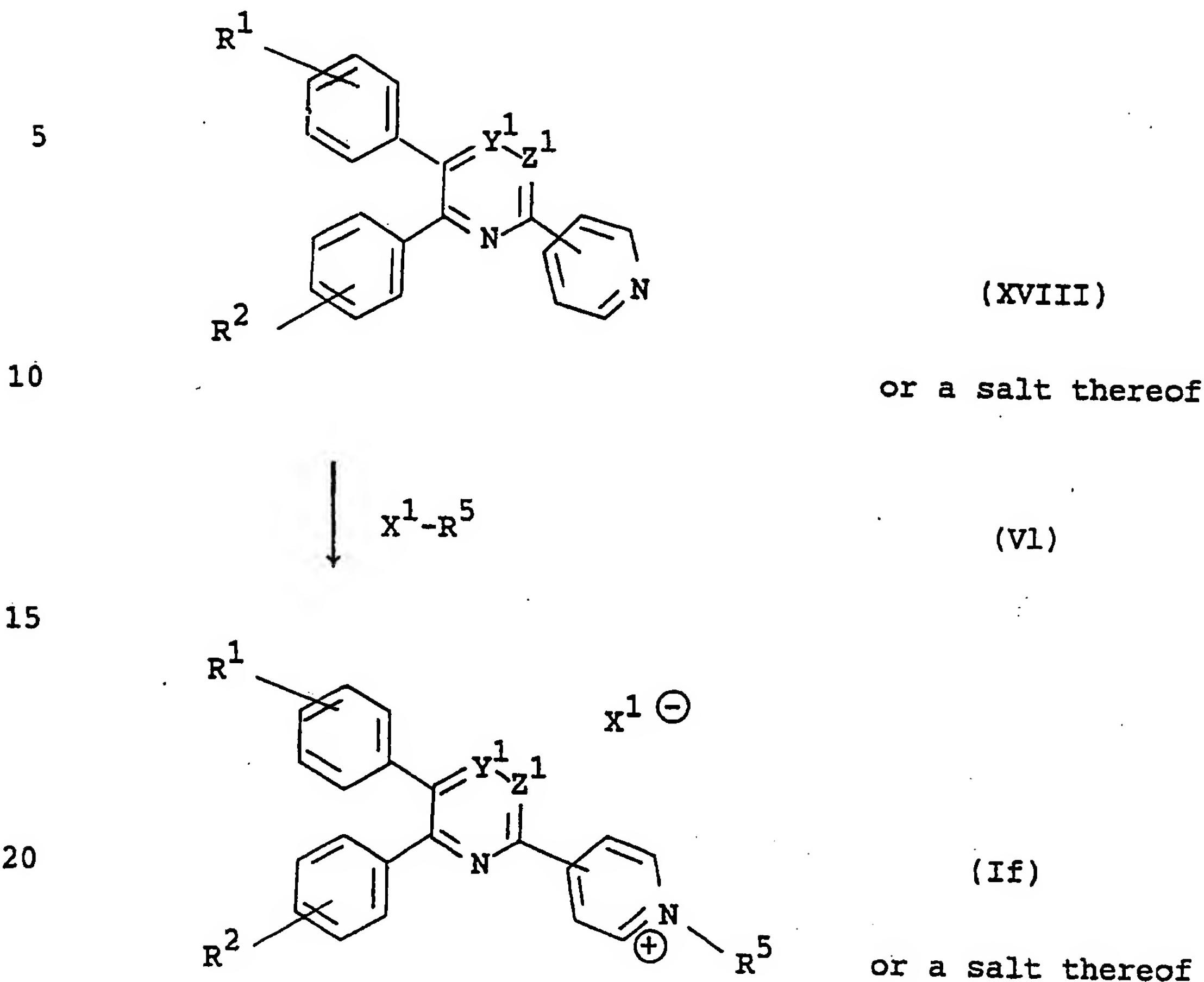


(Ie)

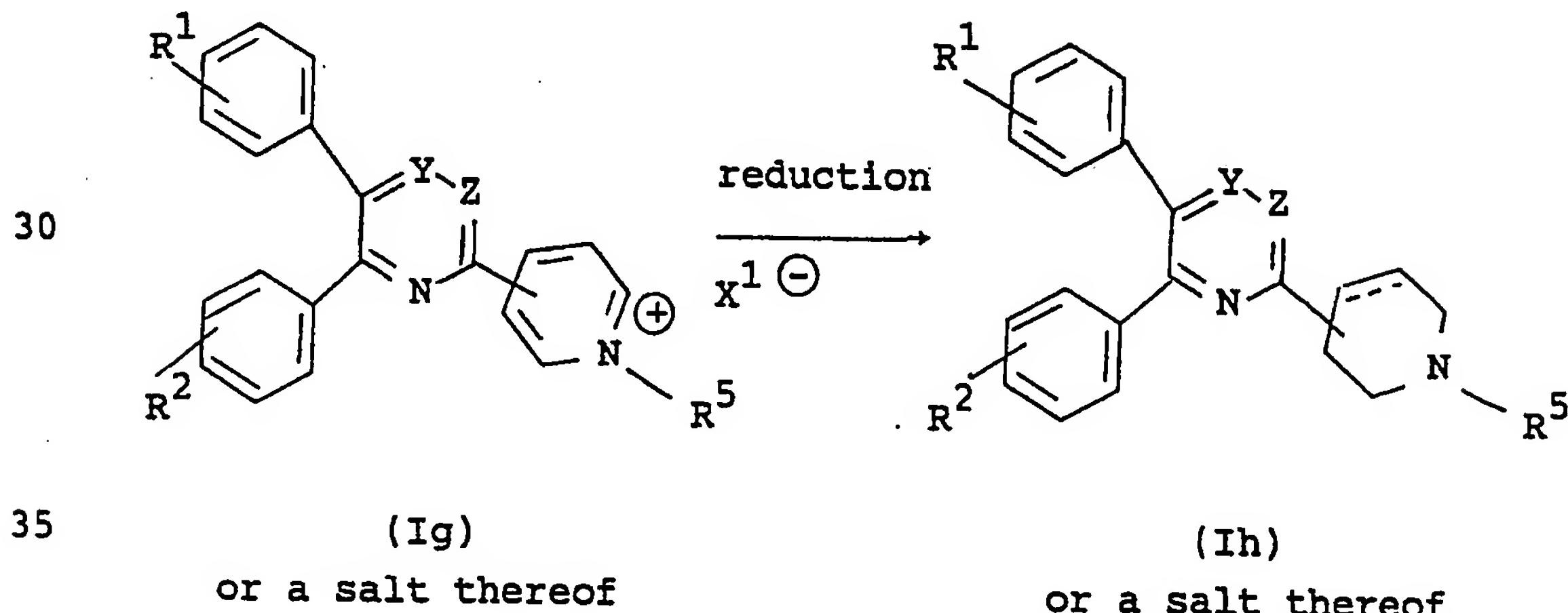
or a salt thereof

- 7 -

Process (5)

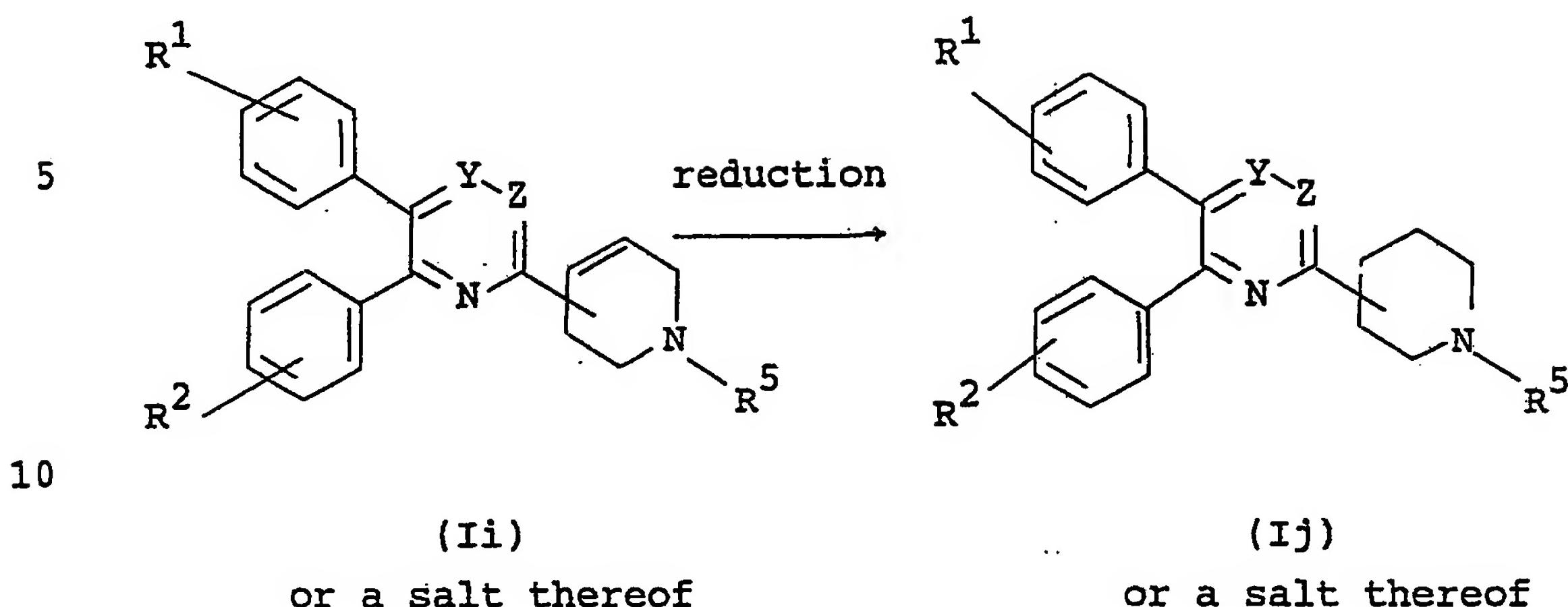


25 Process (6)

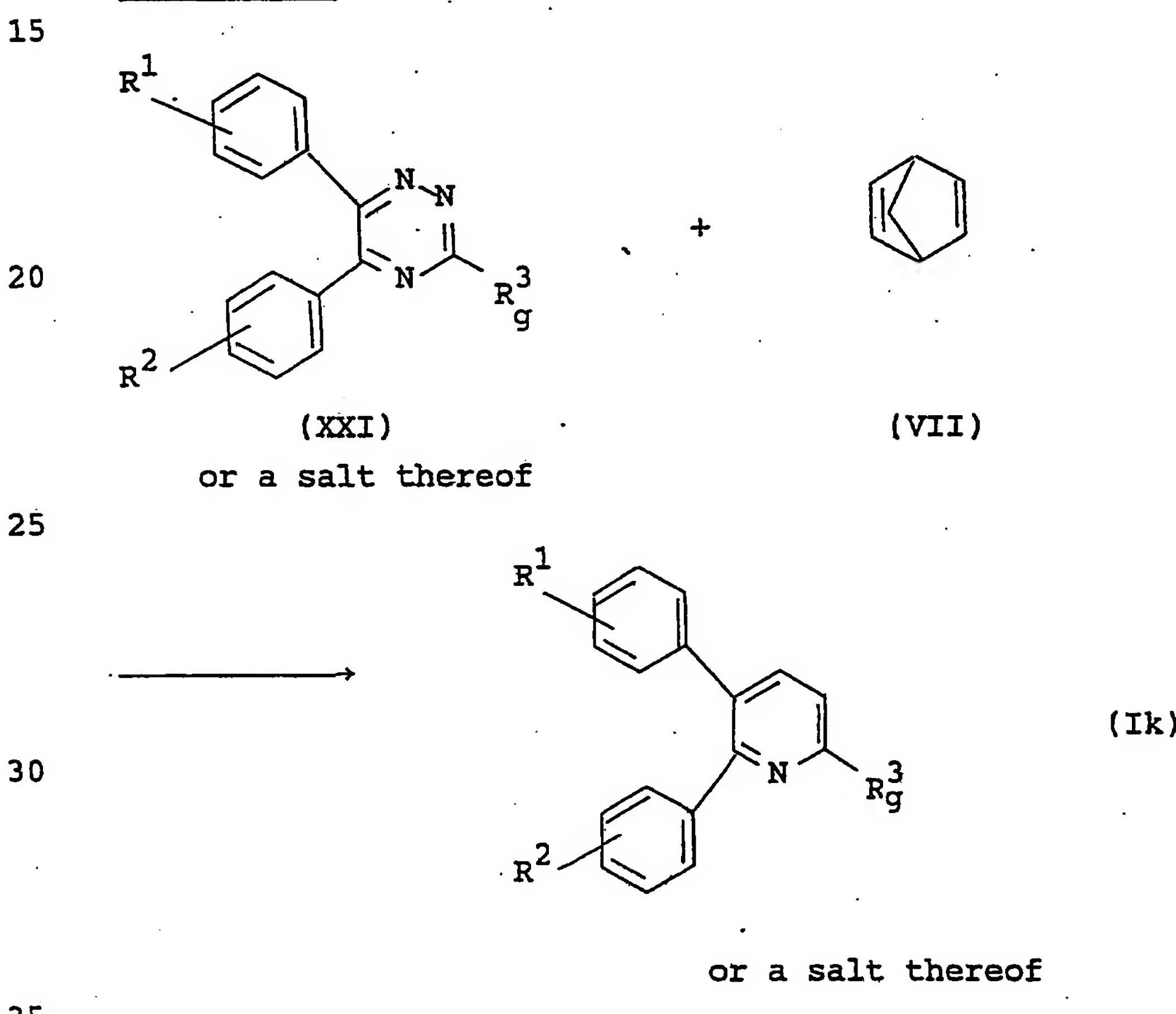


- 8 -

Process (7)

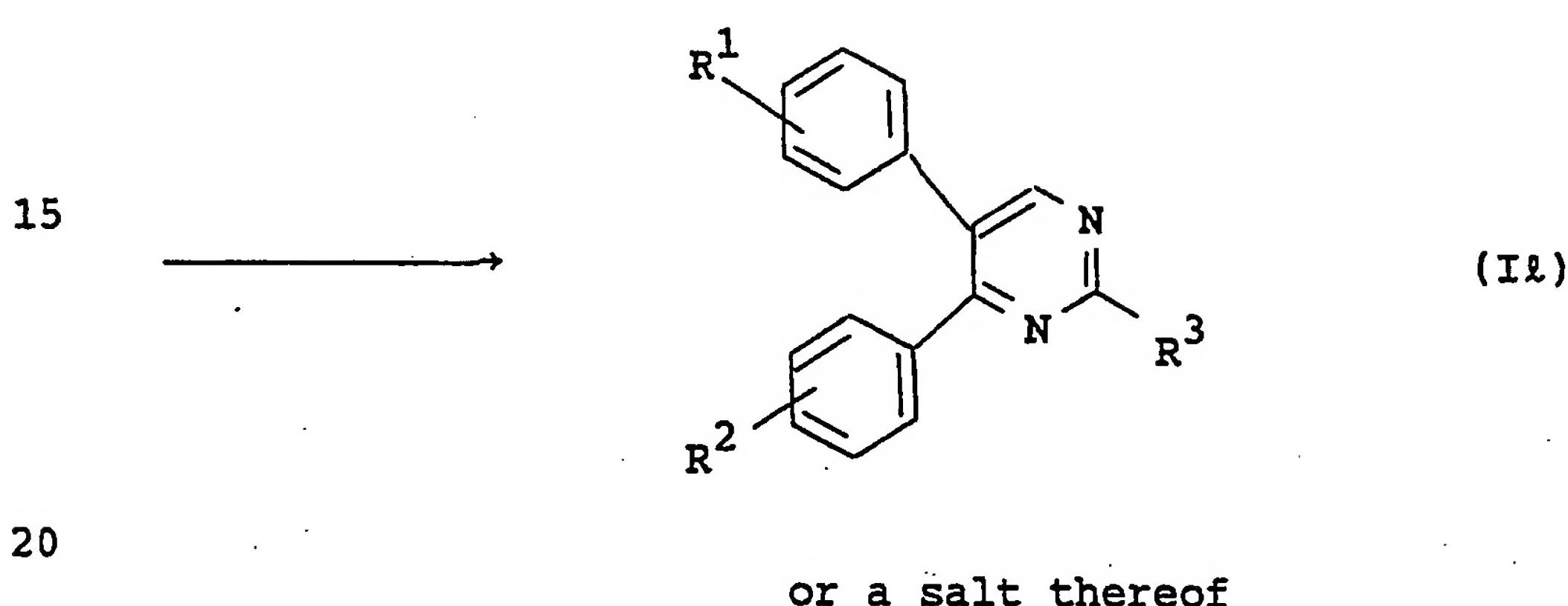
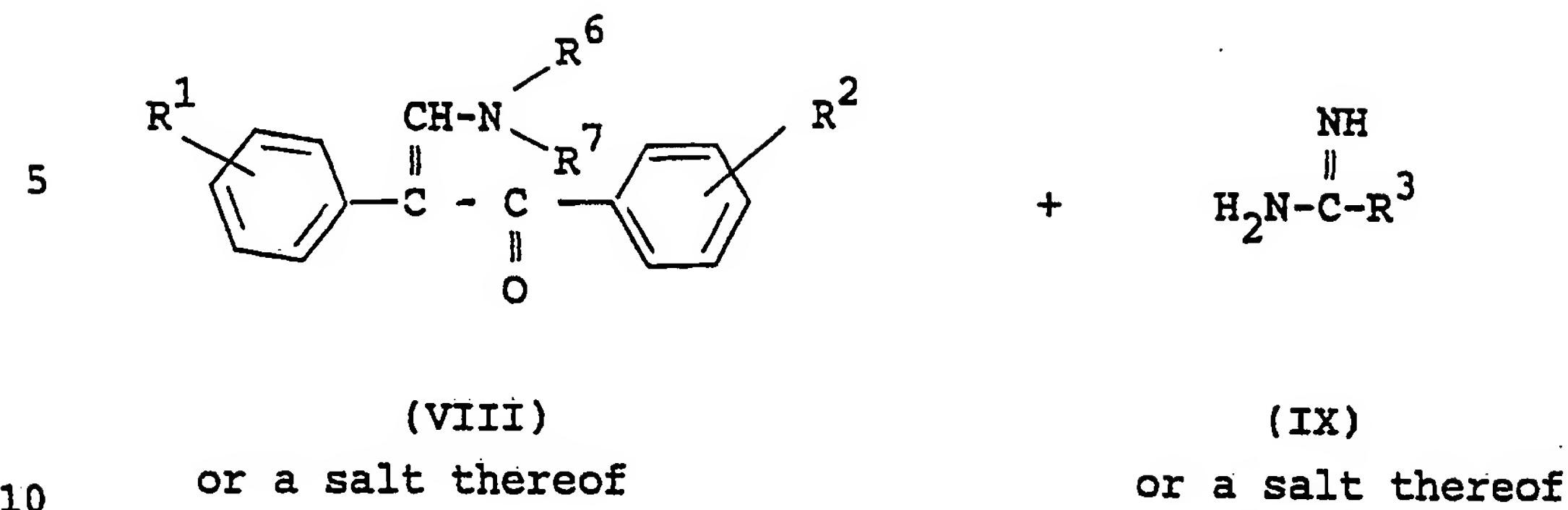


Process (8)

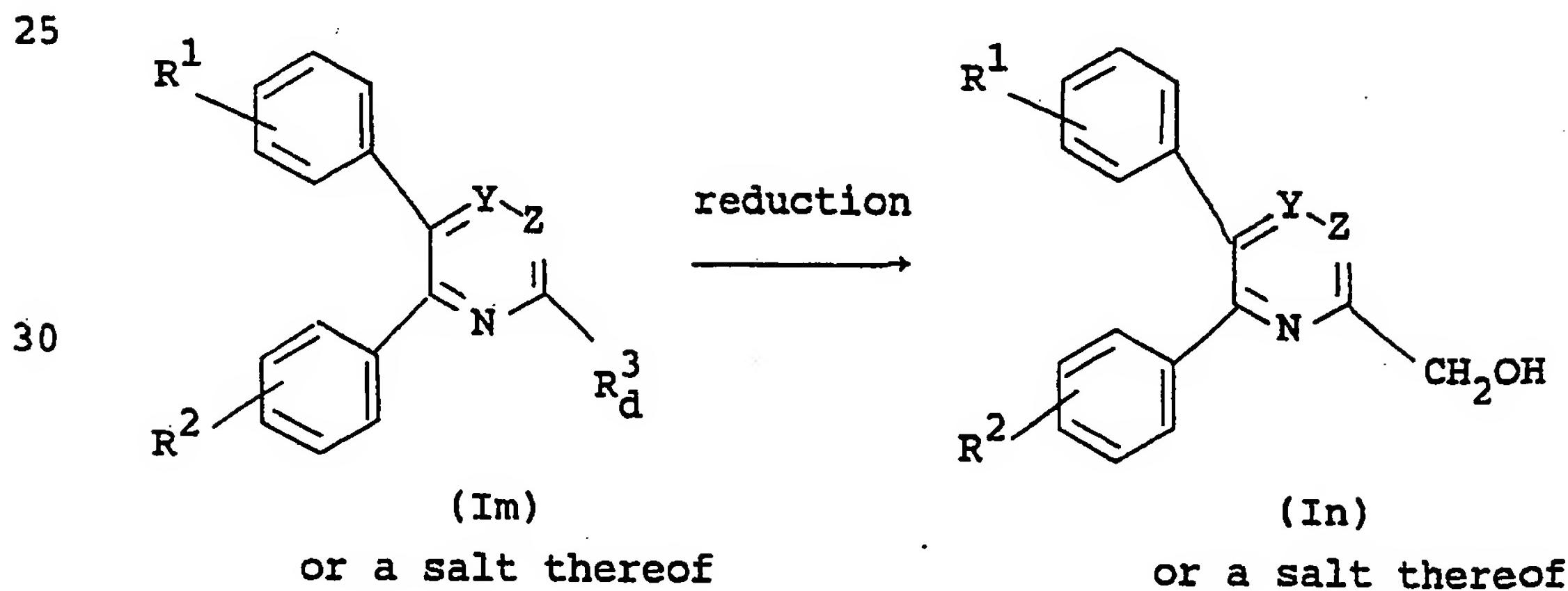


- 9 -

Process (9)



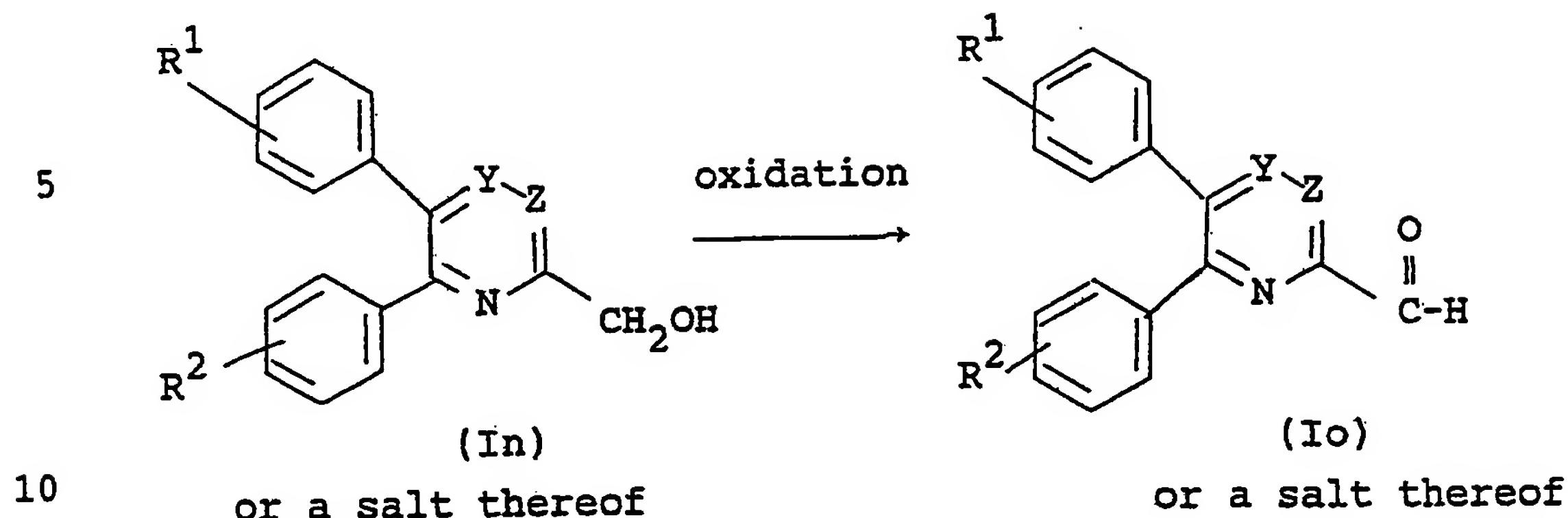
Process (10)



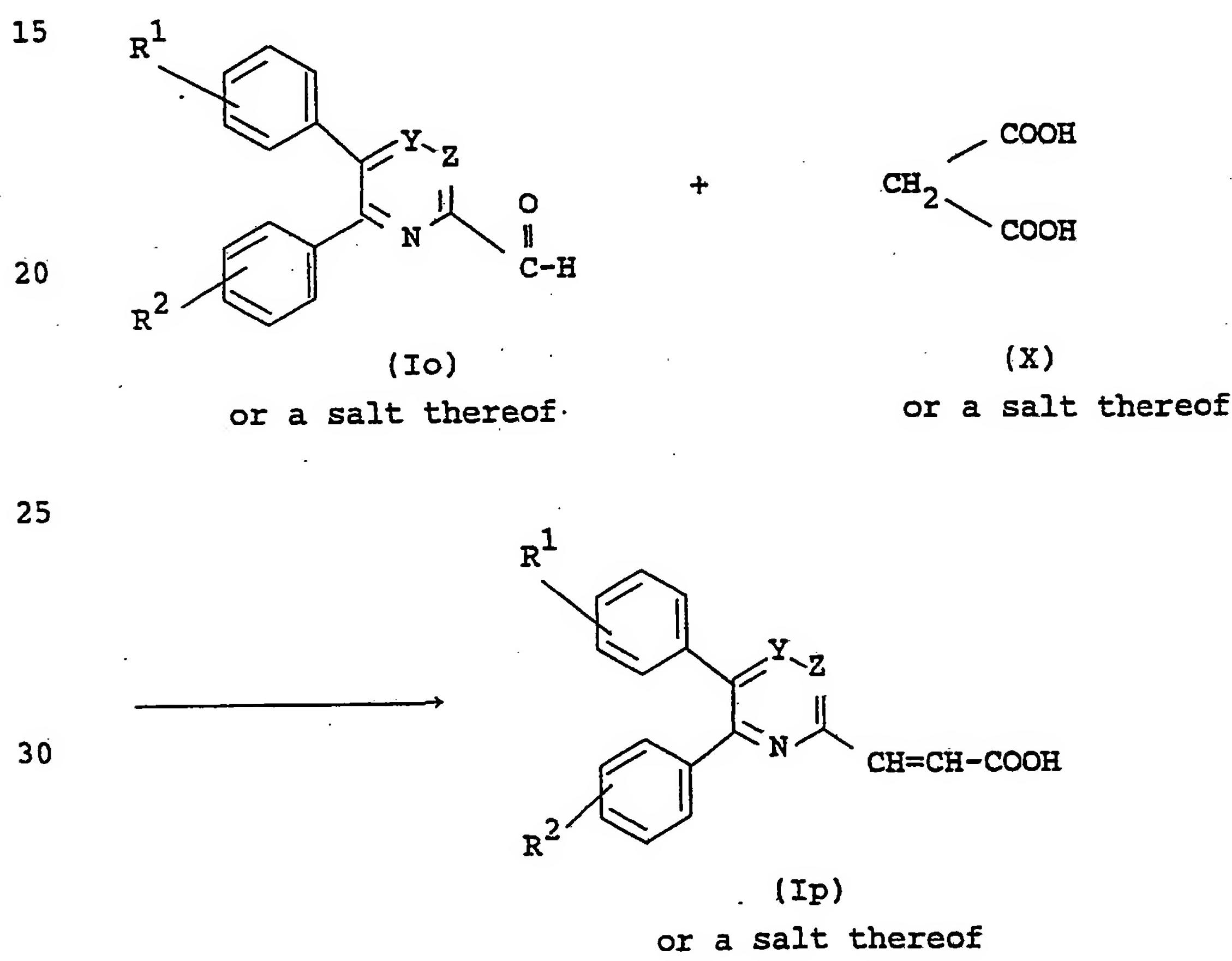
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- 10 -

Process (11)

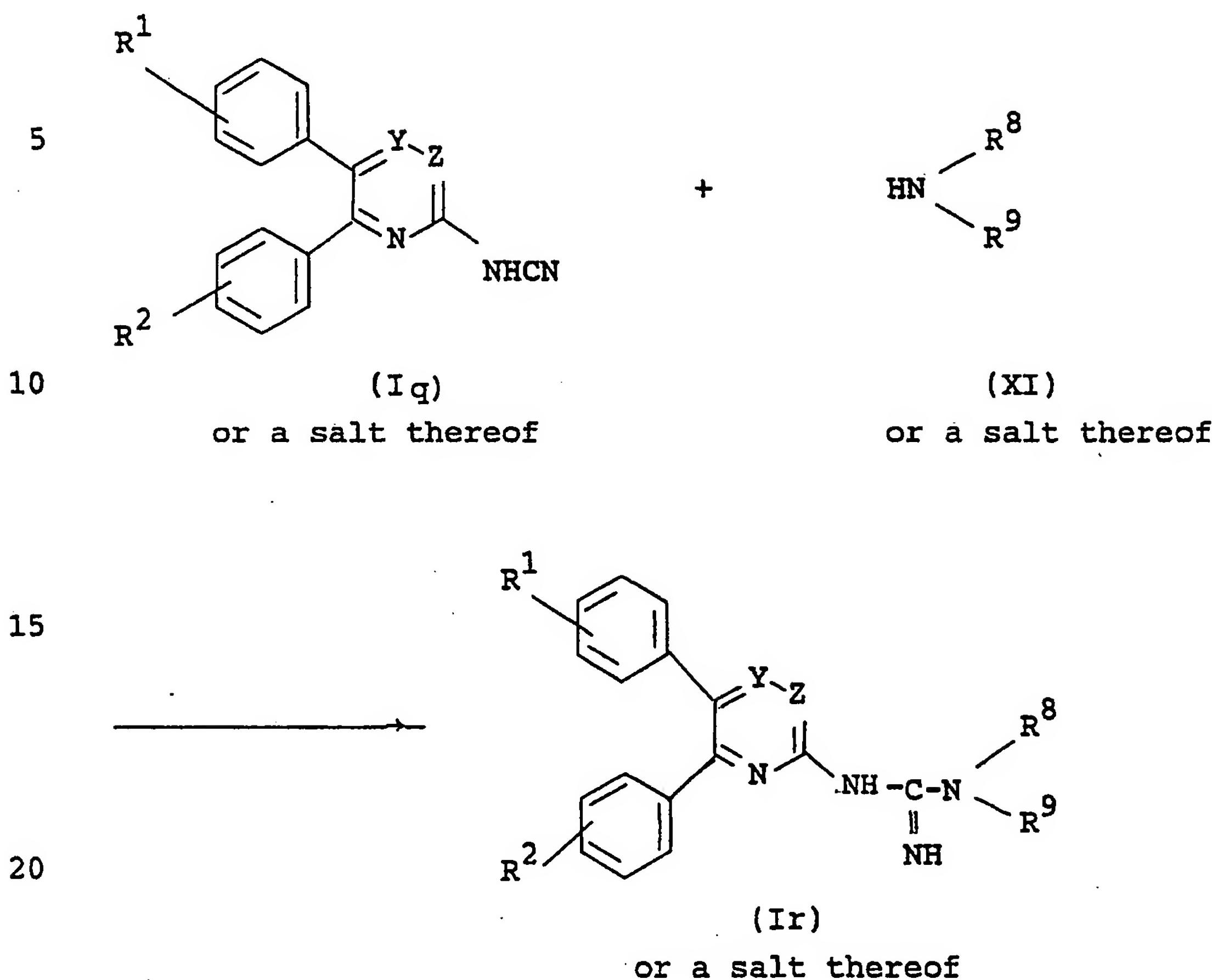


Process (12)

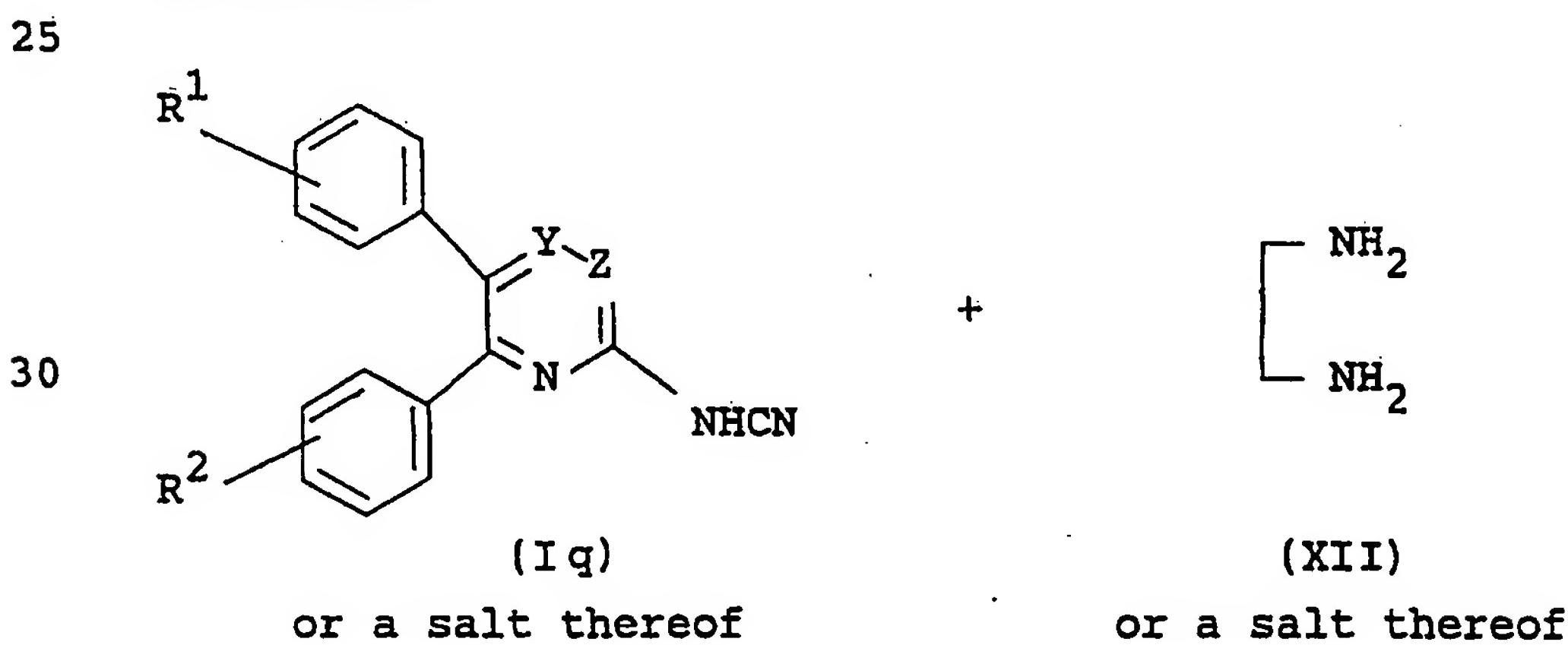


- 11 -

Process (13)

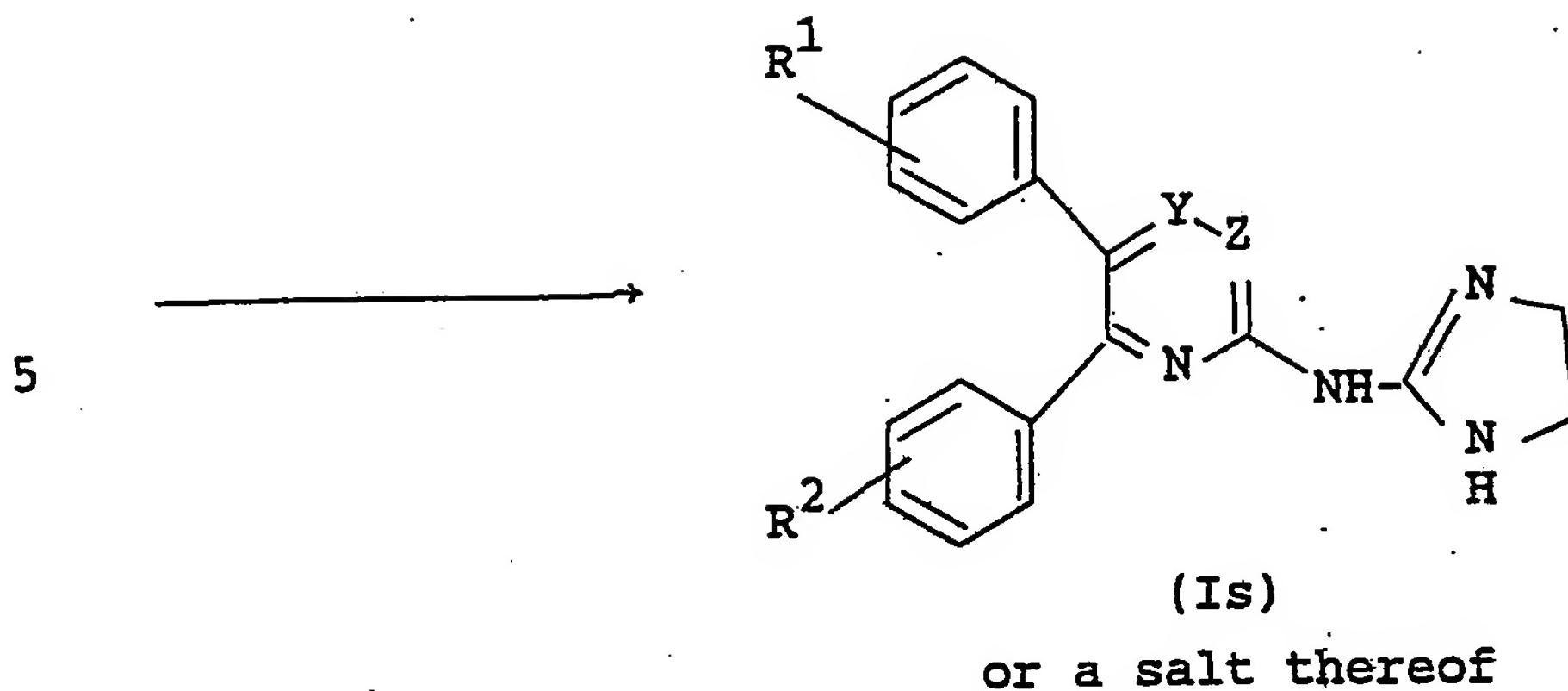


Process 14

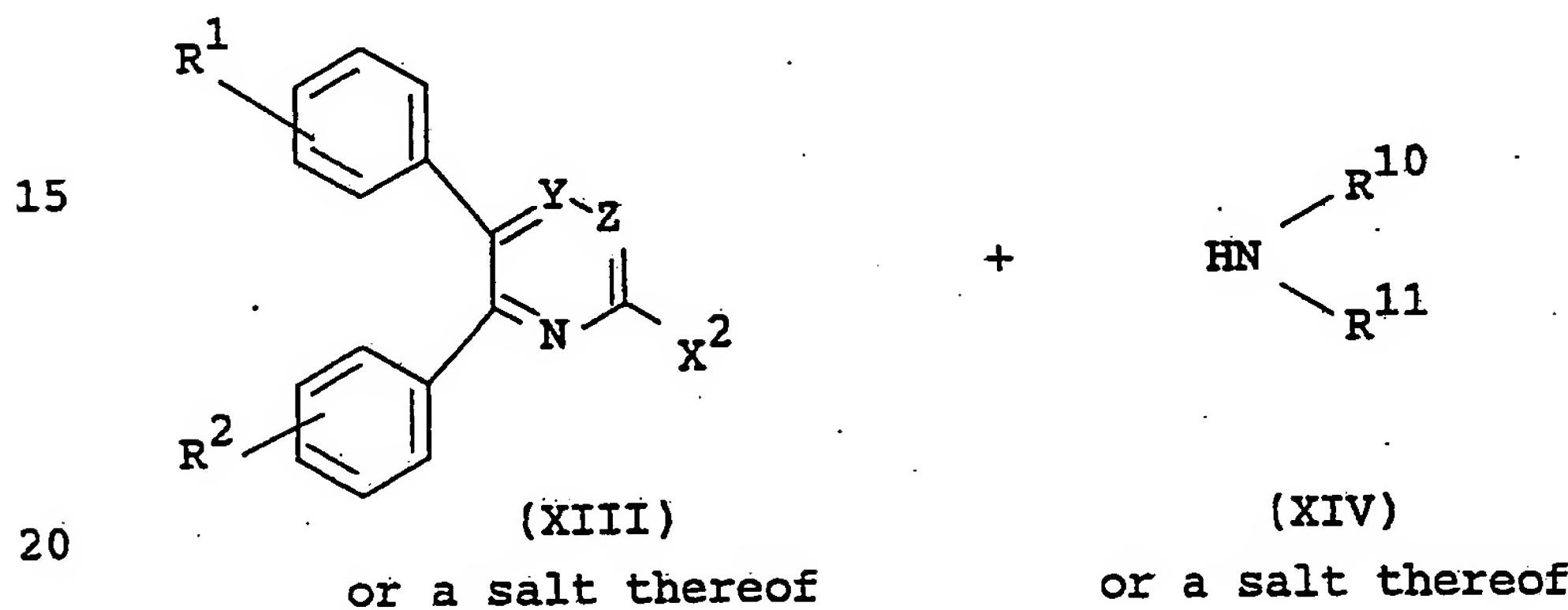


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- 12 -

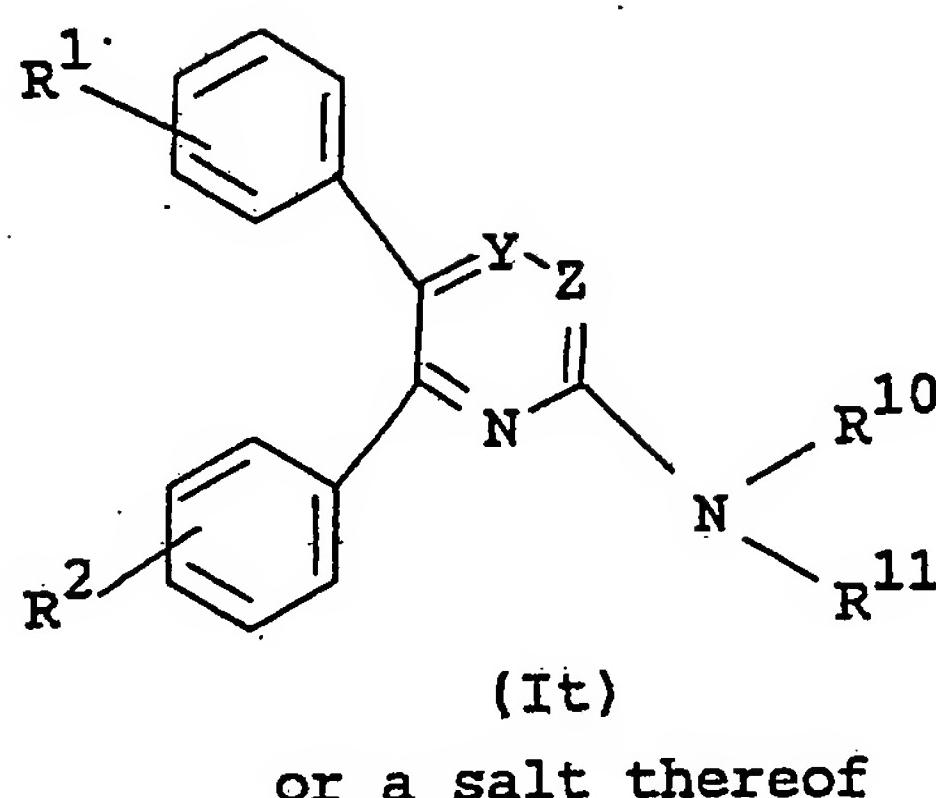


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Process (15)

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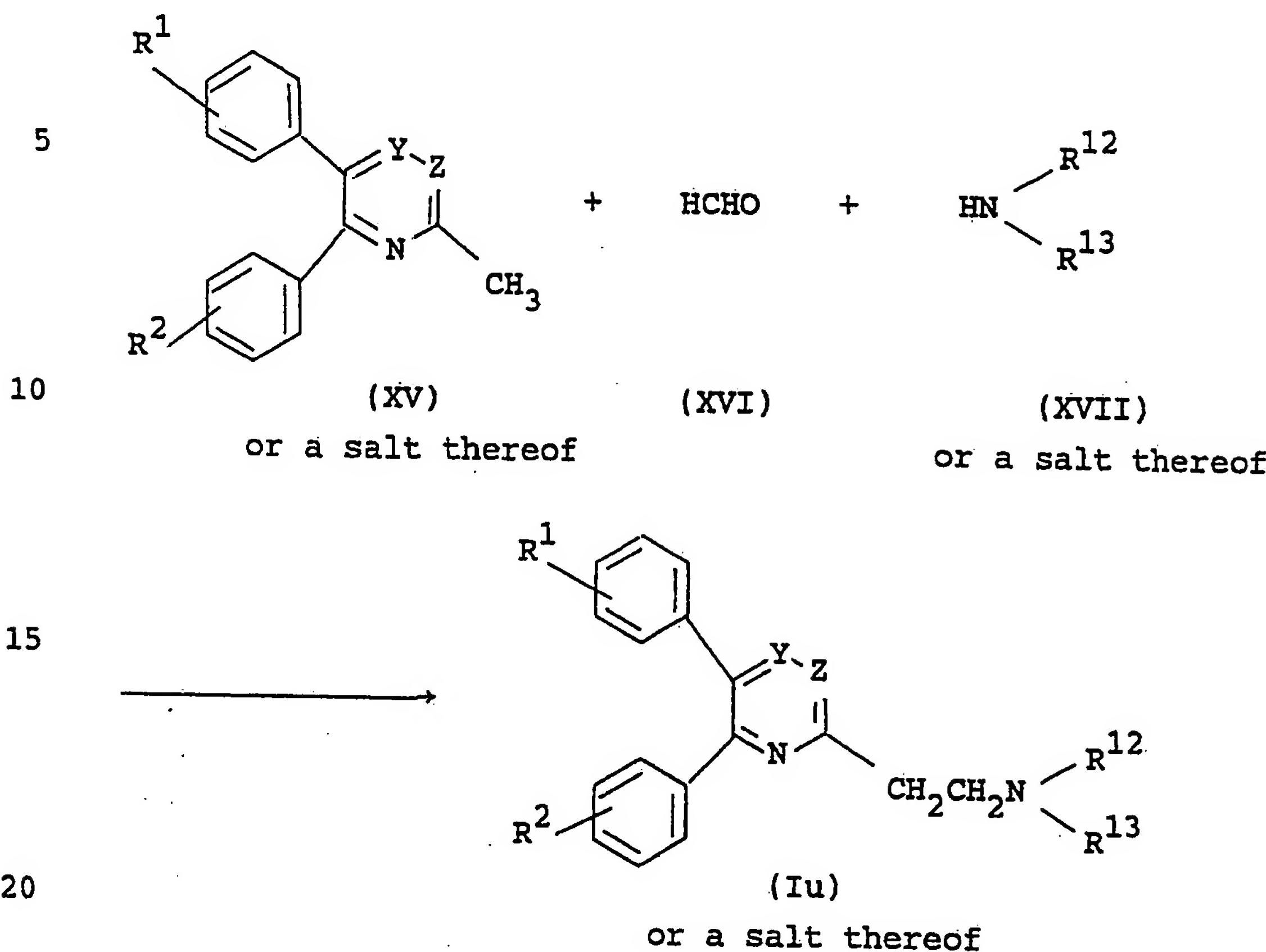
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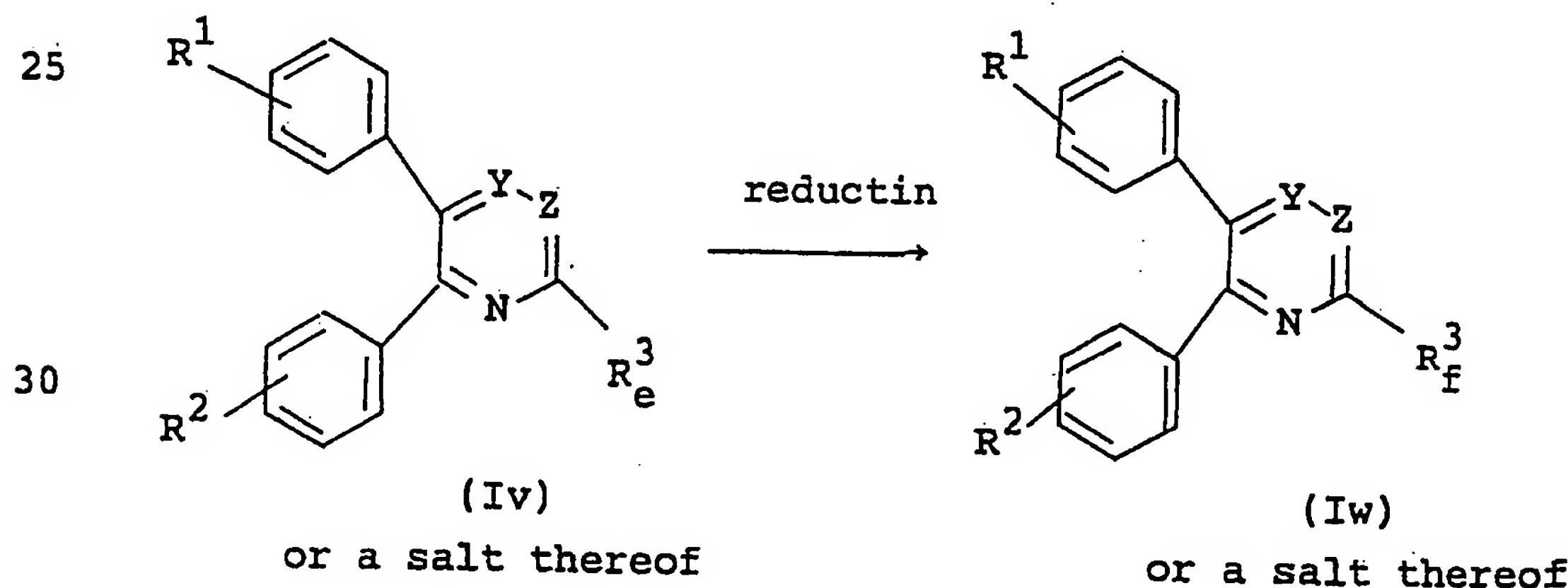
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- 13 -

Process (16)

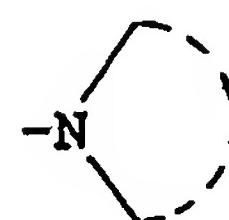


Process (17)



- 14 -

wherein R^1 , R^2 , R^3 , R^5 , y , z and x^1 are each as defined above,



is mono(or di)lower alkylamino,

5

di(lower)alkylamino-(lower)alkylamino,
heterocyclicamino which may have suitable
substituent(s), or heterocyclic group
containing at least one nitrogen atom which
may have suitable substituent(s),

10

R_a^3 is protected amino(lower)alkyl,

R_b^3 is amino(lower)alkyl,

R_c^3 is acylamino(lower)alkyl,

R_d^3 is carboxy or protected carboxy,

15

R^6 and R^7 are each lower alkyl,

R^8 and R^9 are each hydrogen, lower alkyl,

cyclo(lower)alkyl, ar(lower)alkyl,

heterocyclic group which may have suitable
substituent(s), or

20

R^8 and R^9 are linked together with the attached
nitrogen atom to form heterocyclic group
which may have suitable substituent(s),

x^2 is a leaving group,

25

R^{10} is hydrogen or lower alkyl and

R^{11} is lower alkyl or 1-amino-1-iminomethyl, or

R^{10} and R^{11} are linked together with the attached
nitrogen atom to form heterocyclic group
which may have suitable substituent(s),

30

R^{12} and R^{13} are each lower alkyl,

$R_{e_3}^3$ is carboxy(lower)alkenyl,

R_f^3 is carboxy(lower)alkyl,

— in Process (6) means a single or double bond,

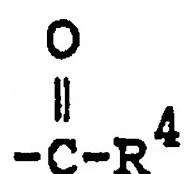
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R_g^3 is heterocyclic group selected from the group
consisting of pyridyl, tetrahydropyridyl,
piperidyl, piperazinyl and morpholinyl,

- 15 -

which may have suitable substituent(s);
substituted amino; carboxy(lower)alkenyl;
carboxy(lower)alkyl; hydroxy(lower)alkyl;
amino(lower)alkyl which may have suitable
substituent(s);

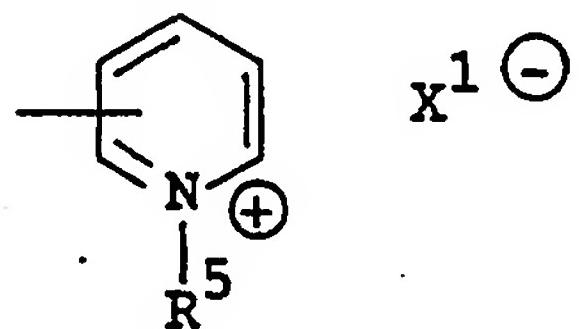
5 a group of the formula :



10

(in which R^4 is hydrogen, ethoxy, mono(or
di)lower alkylamino,
di(lower)alkylamino-(lower)-
alkylamino, heterocyclicamino
which may have suitable
substituent(s), or
heterocyclic group which may
have suitable substituent(s);
or a group of the formula :

20



25

(in which R^5 is lower alkyl or
ar(lower)alkyl which may have
suitable substituent(s), and
 x^1 is an acid residue),

30

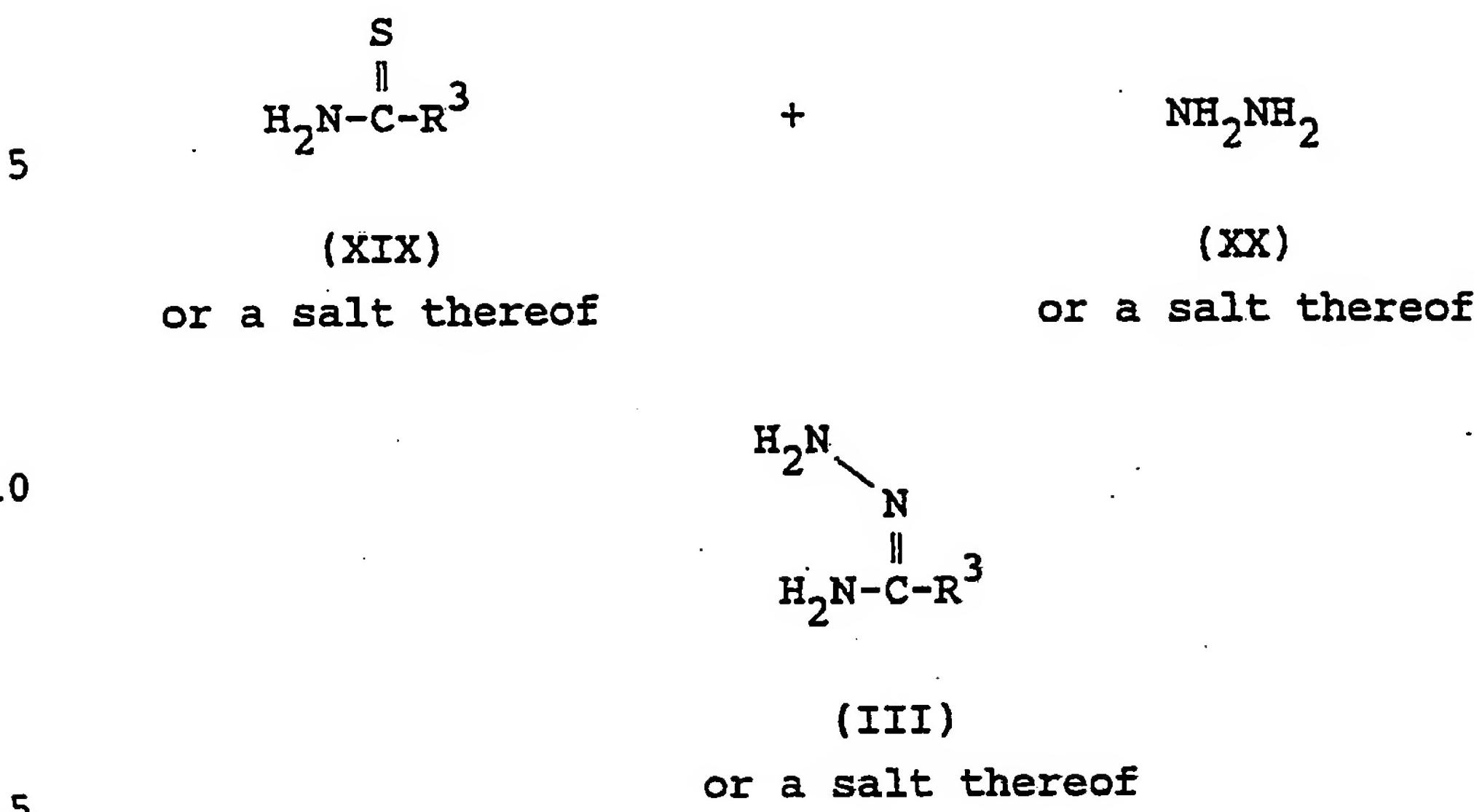
Y^1 is CH or N and
 Z^1 is CH or N.

The starting compound (III) or a salt thereof can be
prepared by the following Processes.

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- 16 -

Process (a)



wherein R^3 is as defined above.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations

of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

5 The term "lower" is intended to mean 1 to 6 carbon atom(s), preferably one having 1 to 4 carbon atom(s), unless otherwise indicated.

10 Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

15 Suitable "substituent" in the term "heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have suitable substituent(s)" may include lower alkyl, ar(lower)alkyl which may have a suitable substituent such as halogen [e.g. fluorine, chlorine, bromine or iodine], and the like.

20 Suitable "lower alkenyl" in the terms "carboxy(lower)alkenyl" and "lower alkenylamino" may include straight or branched one having 2 to 6 carbon atom(s), such as vinyl, propenyl, butenyl, isobut enyl or the like, preferably one having 2 to 4 carbon atom(s).

25 Suitable "substituted amino" may include cyanoamino; imidazolinylamino; guanidino; di(lower)alkylguanidino; lower alkylguanidino; cyclo(lower)alkylguanidino; ar(lower)alkylguanidino; heterocyclicguanidino which may be substituted with suitable substituent(s) such as ar(lower)alkyl or the like; (1-heterocyclic-1-iminomethyl)amino which may have suitable substituent(s) such as lower alkyl, ar(lower)alkyl, aryl which may have suitable substituent(s) such as lower alkoxy or the like, or the like; di(lower)alkylamino; and the like.

30 Suitable "lower alkyl" and "lower alkyl moiety" in the terms "carboxy(lower)alkyl", "hydroxy(lower)alkyl",

"amino(lower)alkyl", "di(lower)alkylamino-(lower)alkylamino", "acylamino(lower)alkyl", "protected amino(lower)alkyl", "di(lower)alkylamino", "di(lower)alkylguanidino", "lower alkylguanidino",
5 "ar(lower)alkyl", "hydroxy(lower)alkylamino", "mono(or di)lower alkylamino", "halophenyl(lower)alkylamino" and "ar(lower)alkylguanidino" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl,
10 pentyl, t-pentyl, hexyl or the like, preferably one having 1 to 4 carbon atom(s).

Suitable "protected amino moiety" in the term "protected amino(lower)alkyl" may include acylamino and the like.

15 Suitable "protected carboxy" may include esterified carboxy and the like.

Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, 20 butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxyethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 25 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxymethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 30 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxyethyl ester, 3,3-dimethylbutyryloxyethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester
35

(e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxy carbonyloxy(lower)alkyl ester (e.g. methoxy-
5 carbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phthalidylidene(lower)alkyl ester, or (5-lower alkyl 2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g.
10 (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.]; lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g. ethynyl ester, propynyl ester,
15 etc.); ar(lower)alkyl ester which may have at least one suitable substituent(s) such as mono(or di or tri)-phenyl(lower)-alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester,
20 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable
25 substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

Suitable "acyl" in the terms "acylamino" and
30 "acylamino(lower)alkyl" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as
35 follows :-

- 20 -

Carbamoyl;

Alliphatic acyl such as lower or higher alkanoyl (e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxy carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, etc.), lower or higher alkanesulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.);

lower or higher alkoxy sulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g. benzoyl, toluoyl, naphthoyl, etc.);

ar(lower) alkanoyl [e.g. phenyl(lower) alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower) alkanoyl (e.g. naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower) alkenoyl [e.g. phenyl(lower) alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower) alkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl, naphthylpentenoyl, etc.), etc.];

ar(lower) alkoxy carbonyl [e.g. phenyl(lower) alkoxy carbonyl (e.g. benzyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g. phenoxy carbonyl, naphthoxy carbonyl, etc.);
aryloxy(lower) alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.);

- 21 -

- arylcaramoyl (e.g. phenylcarbamoyl, etc.);
arylthiocaramoyl (e.g. phenylthiocaramoyl, etc.);
arylglyoxyloyl (e.g. phenylglyoxyloyl, naphthylglyoxyloyl,
etc.);
5 arenesulfonyl (e.g. benzenesulfonyl, p-toluenesulfonyl,
etc.); or the like;
 Heterocyclic acyl such as
 heterocyclic carbonyl;
 heterocyclic (lower) alkanoyl (e.g. thienylacetyl,
10 thienylpropanoyl, thienylbutanoyl, thienylpentanoyl,
 thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl,
 tetrazolylacetyl, etc.);
 heterocyclic(lower) alkenoyl (e.g. heterocyclicpropenoyl,
 heterocyclicbutenoyl, heterocyclicpentenoyl,
15 heterocyclichexenoyl, etc.);
 heterocyclicglyoxyloyl (e.g. thiazolylglyoxyloyl,
 thienylglyoxyloyl, etc.); or the like; in which suitable
 hetetocyclic moiety in the terms "hetetocycliccarbonyl",
 heterocyclic(lower) alkanoyl", heterocyclic(lower) alkenoyl
20 and "heterocyclicglyoxyloyl" as mentioned above means, in
 more detail, saturated or unsaturated, monocyclic or
 polycyclic heterocyclic group containing at least one
 hetero-atom such as an oxygen, sulfur, nitrogen atom and
 the like. And, especially preferable heterocyclic group
25 may be heterocyclic group such as
 unsaturated 3 to 8-membered more preferably 5 or
 6-membered heteromonycyclic group containing 1 to
 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl,
 imidazolyl, pyrazolyl, pyridyl and its N-oxide,
30 dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl,
 tetrahydropyridazinyl (e.g. 2,3,4,5-tetrahydropyridazinyl,
 etc.), triazolyl (e.g. 4H-1,2,4-triazolyl,
 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl
 (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
35 saturated 3 to 8-membered (more preferably 5 or 6-

membered)heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.; unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; saturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.; saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrotiinyl, dihydrotithionyl, etc.; unsaturated condensed heterocyclic group containing 1 to 2

sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.; unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

10 unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.; unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example,

15 benzoxathiinyl, etc. and the like. The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxy, nitro, oxo, lower alkyl (e.g. methyl, ethyl propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.) or the like.

20

Suitable "heterocyclic group" in the terms "heterocyclic group which may have suitable substituent(s)", "(1-heterocyclic-1-iminomethyl)amino" "heterocyclicguanidino" and "heterocyclicamino which may have suitable substituent(s)" can be referred to the ones as mentioned above.

Suitable "substituent" in the term "heterocyclic group which may have suitable substituent(s)" may include lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, etc.) ar(lower)alkyl, hydroxy(lower)alkyl and the like.

Suitable "heterocyclic group" in the definitions " R^8 " and " R^9 " are linked together with the attached nitrogen atom to form heterocyclic group which may have suitable substituent(s)", " R^{10} " and " R^{11} " are linked together with the

attached nitrogen atom to form heterocyclic group which may have suitable substituent(s)" and "heterocyclic group containing at least one nitrogen atom which may have suitable substituent(s)" may include saturated 3 to 5 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.; saturated 3 to 8-membered (more preferably 5 or 10 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc. and the like.

15 Suitable "substituent" in the term "heterocyclicamino which may have suitable substituent(s)" may include ar(lower)alkyl, and the like.

20 Suitable "substituent" in the definitions "R⁸ and R⁹ are linked together with the attached nitrogen atom to form heterocyclic group which may have suitable substituent(s)" and "R¹⁰ and R¹¹ are linked together with the attached nitrogen atom to form heterocyclic group which may have suitable substituent(s)" may include lower alkyl, ar(lower)alkyl, aryl having lower alkoxy, and the like.

25 Suitable "substituent" in the definition "heterocyclic group containing at least one nitrogen atom which may have suitable substituent(s)" may include lower alkyl, ar(lower)alkyl, hydroxy(lower)alkyl, and the like.

30 Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moiety" in the term "cyclo(lower)alkylguanidino" may include 3 to 8-membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 5 to 7 carbon atoms.

35 Suitable "substituent" in the term "amino(lower)alkyl which may have suitable substituent(s)" may include lower

alkyl, acyl as exemplified above, and the like.

Suitable "acid residue" may include halogen as exemplified above.

5 Suitable "leaving group" may include an acid residue as exemplified above, and the like.

Suitable "aryl" and "aryl moiety" in the terms "ar(lower)alkyl" and "ar(lower)alkylguanidino" may include phenyl, naphthyl and the like.

10 Suitable "substituent" in the term "ar(lower)alkyl" which may have suitable substituent(s) may include halogen as exemplified above, and the like.

Suitable "halogen" and "halogen moiety" in the term "halophenyl(lower)alkylamino" is as exemplified above.

15 Preferred embodiments of the object compound (I) are as follows.

R¹ is lower alkoxy,

R² is lower alkoxy,

20 R³ is heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have one to three (more preferably one or two) suitable substituent(s) [more preferably heterocyclic group selected from the group consisting of pyridyl,

25 tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have one or two substituent(s) selected from the group consisting of lower alkyl and ar(lower)alkyl which may have one or two halogen;

30 most preferably heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have one or two substituent(s) selected from the group consisting of lower alkyl, phenyl(lower)alkyl and halophenyl(lower)alkyl];

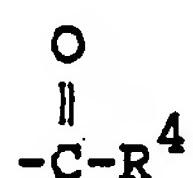
- 26 -

cyanoamino; imidazolinylamino; guanidino;
di(lower)alkylguanidino; lower alkylguanidino;
cyclo(lower)alkylguanidino; ar(lower)alkylguanidino
[more preferably phenyl(lower)alkylguanidino];
5 heterocyclicguanidino which may be substituted with
one to three (more preferably one) suitable
substituent(s) [more preferably heterocyclicguanidino
which may have ar(lower)alkyl; most preferably
phenyl(lower)alkylpiperidylguanidino];
10 (1-heterocyclic-1-iminomethyl)amino which may have
one to three (more preferably one) suitable
substituent(s) [more preferably
(1-heterocyclic-1-iminomethyl)amino which may have
substituent selected from the group consisting of
15 lower alkyl, ar(lower)alkyl and aryl which may have
lower alkoxy; most preferably
{morpholinyl(imino)methyl}amino,
{piperidyl(imino)methyl}amino which may have
phenyl(lower)alkyl, or
20 {piperazinyl(imino)methyl}amino which may have
substituent selected from the group consisting of
lower alkyl, phenyl(lower)alkyl and lower alkoxy
phenyl]; di(lower)alkylamino; hydroxy(lower)alkyl;
carboxy(lower)alkyl; carboxy(lower)alkenyl;
25 amino(lower)alkyl which may have one to three (more
preferably one or two) substituent(s) selected from
the group consisting of lower alkyl and acyl [more
preferably amino(lower)alkyl which may have one or
two substituent(s) selected from the group consisting
30 of lower alkyl, lower alkanoyl, lower alkylcarbamoyl,
lower alkoxycarbonyl and heterocycliccarbonyl which
may have one to three suitable substituent(s); most
preferably amino(lower)alkyl which may have one or
two substituent(s) selected from the group consisting
35 of lower alkyl, lower alkanoyl, lower alkylcarbamoyl,

- 27 -

lower alkoxycarbonyl and tetrahydropyridazinyl-carbonyl which may have oxo group];
a group of the formula :

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10

(in which R^4 is hydrogen, ethoxy, mono(or di)lower alkylamino,
di(lower)alkylamino-(lower)alkylamino,
heterocyclicamino which may have one
to three (more preferably one or two)
substituent(s) selected from the group
consisting of lower alkyl, lower
alkoxy, halogen and ar(lower)alkyl
[more preferably saturated 5 or
6-membered heteromonocyclicamino in
which heteromonocyclic group contains
1 to 3 nitrogen atom(s), which may
have one or two substituent(s)
selected from the group consisting of
lower alkyl, lower alkoxy halogen and
phenyl(lower)alkyl; most preferably
phenyl(lower)alkylpiperidylamino] or
heterocyclic group which may have one
to three (more preferably one or two)
substituent(s) selected from the group
consisting of lower alkyl, lower
alkoxy, halogen, ar(lower)alkyl and
hydroxy(lower)alkyl [more preferably
saturated 5 or 6-membered
heteromonocyclic group containing 1 to
2 oxygen atom(s) and 1 to 3 nitrogen
atom(s), which may have one or two
substituent(s) selected from the group

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- 28 -

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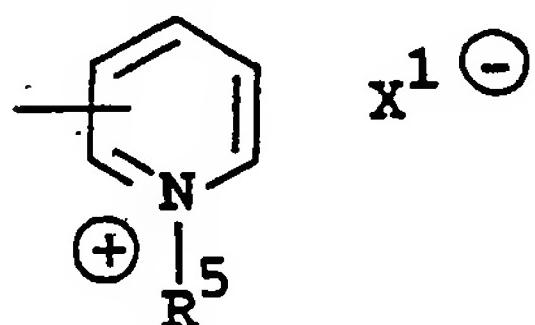
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consisting of lower alkyl, lower alkoxy, halogen, phenyl(lower)alkyl and hydroxy(lower)alkyl, or saturated 5 or 6-membered heteromonocyclic group containing 1 to 3 nitrogen atom(s), which may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen, phenyl(lower)alkyl and hydroxy(lower)alkyl; most preferably morpholinyl, or piperazinyl which may have lower alkyl, hydroxy(lower)alkyl or phenyl(lower)alkyl];

or a group of the formula :



(in which R⁵ is lower alkyl, or ar(lower)alkyl which may have one to three (more preferably one or two) substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy [more preferably phenyl(lower)alkyl which may have one or two substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy; most preferably phenyl(lower)alkyl which may have halogen], and
x¹ is an acid residue [more preferably halogen]),

y is CH or N and

Z is CH or N,
with proviso that
when R³ is pyridyl; piperidyl which may have hydroxy
group; piperazinyl which has lower alkyl group
5 or hydroxy(lower)alkyl group; morpholinyl; lower
alkenylamino; hydroxy(lower)alkylamino;
phenylamino which may have lower alkoxy group or
halogen on the benzene ring;
halophenyl(lower)alkylamino; phenylsulfonylamino
10 which has nitro group, amino group or halogen on
the benzene ring; or amino substituted with two
substituents selected from the group consisting
of lower alkyl and hydroxy(lower)alkyl, and
Y is N,
15 then Z is CH.

The processes for preparing the object and starting
compounds are explained in detail in the following.

20 Process (1)

The compound (Ia) or a salt thereof can be prepared
by reacting the compound (II) with the compound (III) or a
salt thereof.

The reaction is usually carried out in a conventional
25 solvent such as water, alcohols (e.g., methanol, ethanol,
isopropyl alcohol, etc.), tetrahydrofuran, dioxane,
chloroform, methylene chloride, dimethyl acetamide,
N,N-dimethylformamide or any other organic solvent which
does not adversely influence the reaction. Among these
30 solvents, hydrophilic solvents may be used in a mixture
with water.

This reaction is preferably carried out in the
presence of an inorganic or an organic acid such as
hydrochloric acid, hydrobromic acid, sulfuric acid, etc.),
35 an organic acid (e.g. formic acid, acetic acid,

- 30 -

trifluoroacetic acid, propionic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), and the like.

The reaction may be also carried out in the presence 5 of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, 10 N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

The reaction temperature is not critical and the 15 reaction is usually carried out under cooling to heating.

Suitable salts of the compounds (III) and (Ia) can be referred to the ones as exemplified for the compound (I).

Process (2)

20 The compound (Ib) or a salt thereof can be prepared by reacting a compound (IV) or its reactive derivative at the carboxy group or a salt thereof with a compound (V) or a salt thereof.

As suitable said reactive derivatives at the carboxy 25 group, there may be mentioned acid halides, acid anhydrides, active amides and esters. Suitable examples are acid halides such as acid chloride and acid bromide, mixed acid anhydrides with various acids [e.g. substituted phosphoric acid such as dialkyl phosphoric acid, sulfuric acid, aliphatic carboxylic acid, aromatic carboxylic acid, etc.], symmetric acid anhydrides, active amides with various imidazoles, and esters such as lower alkyl ester [e.g. methyl ester, ethyl ester, etc.], cyanomethyl ester, methoxymethyl ester, p-nitrophenyl ester, 30 2,4-dinitrophenyl ester, pentachlorophenyl ester,

- 31 -

phenylazophenyl ester, carboxymethylthio ester, and N-hydroxysuccinimide ester.

The reaction is usually carried out in a conventional solvent, such as methylene chloride, chloroform, alcohol [e.g. methanol, ethanol, etc.], benzene, toluene, pyridine, diethyl ether, dioxane, tetrahydrofuran, acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide or any other organic solvent which does not adversely affect the reaction. In case that the compound (V) is liquid, it can also be used as a solvent.

The reaction temperature is not critical and the reaction can be carried out under cooling, at ambient temperature, or under heating.

This reaction can typically be conducted in the presence or absence of an accelerator such as base.

Suitable base may include a tertiary amine [e.g. triethylamine, pyridine, N,N-dimethylaniline, etc.], an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], alkali metal bicarbonate [e.g. sodium bicarbonate, etc.], a salt of an organic acid [e.g. sodium acetate, etc.] and the like. In case that the base is liquid, the base can be used as a solvent.

Suitable salts of the compounds (IV), (V) and (Ib) can be referred to the ones as exemplified for the compound (I).

Process (3)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to elimination reaction of the amino-protective group on R³_a. Suitable method of this reaction may include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid,

trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g.

5 platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

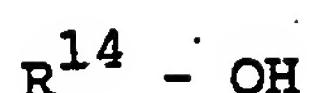
25 Suitable salts of the compounds (Ic) and (Id) can be referred to the ones as exemplified for the compound (I).

Process (4)

30 The compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or its reactive derivative at the amino group or a salt thereof to acylation reaction.

35 Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :

- 34 -



(XXII)

(wherein R^{14} is acyl)

5 or its reactive derivative or a salt thereof.

Suitable reactive derivative at the amino group of the compound (Id) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (Id) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (Id) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (Id) with phosphorus trichloride or phosgene, and the like.

10 Suitable salts of the compound (Id) and (Ie) can be referred to the ones as exemplified for the compound (I).

15 Suitable reactive derivative of the compound (XXII) may include an acid halide, an acid anhydride, an activated amide, an activated ester, isocyanate, and the like. The suitable example may be an acid chloride an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole,

triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [(CH₃)₂N=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); substituted or unsubstituted aryl isocyanate; substituted or unsubstituted aryl isothiocyanate, and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (XXII) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (XXII) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine;

ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; 5 triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with 10 thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, 15 N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

20 Process (5)

The compound (If) or a salt thereof can be prepared by reacting the compound (XVIII) or a salt thereof with the compound (VI).

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these 25 solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Suitable salts of the compounds (XVIII) and (If) can 35 be referred to the ones as exemplified for the compound (I).

Process (6)

The compound (Ih) or a salt thereof can be prepared by subjecting the compound (Ig) or a salt thereof to reduction.

5 Reduction is carried out in a conventional manner including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, etc.) or a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like.

30 The reduction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, etc.), N,N-dimethylformamide, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely affect the reaction.

35 Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can

also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

5 Suitable salts of the compounds (Ig) and (Ih) can be referred to the ones as exemplified for the compound (I).

Process (7)

10 The compound (Ij) or a salt thereof can be prepared by subjecting the compound (Ii) or a salt thereof to reduction as explained in Process (6).

Suitable salts of the compounds (Ii) and (Ij) can be referred to the ones as exemplified for the compound (I).

15 Process (8)

The compound (Ik) or a salt thereof can be prepared by reacting the compound (XXI) or a salt thereof with the compound (VII).

20 The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, xylene, 2-methoxyethanol, N,N-dimethylformamide or any other organic solvent which does not adversely influence 25 the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Suitable salts of the compounds (Ik) and (XXI) can be referred to the ones as exemplified for the compound (I).

30

Process (9)

The compound (Il) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (IX) or a salt thereof.

35

This reaction is usually carried out in a

conventional solvent as exemplified in Process (8).

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence
5 of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, alkali metal methoxide, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.),
10 N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Suitable salts of the compound (VIII) can be referred
15 to the acid addition salts as exemplified for the compound (I).

Suitable salts of the compounds (IX) and (II) can be referred to the ones as exemplified for the compound (I).

20 Process (10)

The compound (In) or a salt thereof can be prepared by subjecting the compound (Im) or a salt thereof to reduction.

Reduction is carried out in a conventional manner,
25 including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, etc.), or a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

35 Suitable catalysts to be used in catalytic reduction

- 40 -

are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, 5 palladium oxide, palladium on carbon, colloidal palladium palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence 10 the reaction such as methanol, ethanol, propanol, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they 15 can also be used as a solvent.

The reaction temperature of this reduction is not 20 critical and the reaction is usually carried out under cooling to heating.

Suitable salts of the compound (Im) can be referred to the ones as exemplified for the compound (I).

25 Process (11)

The compound (Io) or a salt thereof can be prepared by subjecting the compound (In) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, 30 which is capable of oxidizing a hydroxymethyl group to a formyl group, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, etc.), peroxy acid such as peroxybenzoic acid (e.g. peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), magnese dioxide, 35 and the like.

The reaction is usually carried out in a conventional solvent as exemplified in Process (8), or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may 5 be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Suitable salts of the compounds (In) and (Io) can be referred to the acid addition salts as exemplified for the 10 compound (I).

Process (12)

The compound (Ip) or a salt thereof can be prepared by reacting the compound (Io) or a salt thereof with the 15 compound (X) or a salt thereof.

The reaction is usually carried out in a conventional solvent as exemplified in Process (8), or any other organic solvent which does not adversely influence the reaction.

20 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal 25 carbonate, alkali metal acetate, tri(lower)alkylamine, piperidine, piperazine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base 30 and/or the starting compound are in liquid, they can be used also as a solvent.

Suitable salts of the compound (X) can be referred to the base salts as exemplified for the compound (I).

Suitable salts of the compound (Ip) can be referred 35 to the ones as exemplified for the compound (I).

Process (13)

The compound (Ir) or a salt thereof can be prepared by reacting the compound (Iq) or a salt thereof with the compound (XI) or a salt thereof.

5 The reaction is usually carried out in a conventional solvent as exemplified in Process (8), or any other organic solvent which does not adversely influence the reaction.

10 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. In case that the compound (XI) is liquid, it can be used as a solvent.

15 Suitable salts of the compounds (Ir) and (XI) can be referred to the ones as exemplified for the compound (I).

Process (14)

The compound (Is) or a salt thereof can be prepared by reacting the compound (Iq) or a salt thereof with the compound (XII) or a salt thereof.

20 The reaction is usually carried out in a conventional solvent as exemplified in Process (8), or any other organic solvent which does not adversely influence the reaction.

25 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. In case that the compound (XII) is liquid, it can be used as a solvent.

30 Suitable salts of the compound (Iq), (Is) and (XII) can be referred to the acid addition salts as exemplified for the compound (I)..

Process (15)

35 The compound (It) or a salt thereof can be prepared by reacting the compound (XIII) or a salt thereof with the compound (XIV) or a salt thereof.

The reaction is usually carried out in a conventional solvent as exemplified in Process (8), or any other organic solvent which does not adversely influence the reaction.

5 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Suitable salts of the compounds (XIII), (XIV) and (It) can be referred to the ones as exemplified for the compound (I).

10

Process (16)

The compound (Iu) or a salt thereof can be prepared by reacting the compound (XV) or a salt thereof with the compound (XVI) and the compound (XVII) or a salt thereof.

15 The reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, ethylene glycol, etc.), chloroform, ether, tetrahydrofuran, benzene or any other organic solvent which does not adversely influence the reaction.

20 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction is usually carried out in the presence of an acid.

25 Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.). When the acid is liquid, it can be used also as a solvent.

30 Suitable salts of the compounds (XV) (XVII) and (Iu) can be referred to the acid addition salts as exemplified for the compound (I).

Process (17)

35 The compound (Iw) or a salt thereof can be prepared by subjecting the compound (Iv) or a salt thereof to

reduction as explained in Process (10).

Suitable salts of the compounds (Iw) and (Iv) can be referred to the ones as exemplified for the compound (I).

5 Process (a)

The compound (III) or a salt thereof can be prepared by the compound (XIX) or a salt thereof with the compound (XX) or a salt thereof.

10 This reaction can be carried out in the presence or absence of a conventional solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

15 Suitable salts of the compound (XX) can be referred to the acid addition salts as exemplified for the compound (I).

20 Suitable salts of the compounds (XIX) and (III) can be referred to the ones as exemplified for the compound (I).

25 The new heterocyclic compounds (I) and a pharmaceutically acceptable salt thereof of the present invention possess strong antithrombotic activity inhibiting the activities against cyclooxygenase, thrombin, phosphodiesterase and the like, and/or inhibiting aggregation of platelet; vasodilating activity; and anti-inflammatory activity; particularly antithrombotic activity, and therefore are useful as antithrombotic agent, vasodilating agent, and anti-inflammatory agent, particularly anti-thrombotic agent.

30 Accordingly, the new heterocyclic compounds (I) and a pharmaceutically acceptable salt thereof can be used for prophylactic and therapeutic treatment of cerebral thrombosis, atrophic thrombosis; coronary thrombosis; creeping thrombosis; dilation thrombosis; jumping thrombosis; mural thrombosis; placental thrombosis;

- 45 -

platelet thrombosis; posttraumatic arterial thrombosis; thrombostasis; compression thrombosis; peripheral vascular disorders such as chronic arterial occlusion; transient ischemic attack; myocardial infarction; cerebral infarction; reocclusion after percutaneous transluminal coronary angioplasty or percutaneous transluminal coronary recanalization; arteriosclerosis; cerebral vasospasm; disseminated intravascular coagulopathy; hypertension such as pulmonary hypertension; psoriasis; arthritis; nephritis; inflammatory bowel diseases; septic shock; dysmnesia; senile dementia; endotoxin shock; and the like.

And, these compounds are also useful for inhibition of thrombosis during extracorporeal circulation such as dialysis.

Further, these compounds are also expected to have antipyretic activity, analgesic activity, antiviral activity, antifungal activity, anti-allergic activity, 5-lipoxygenase inhibitory activity and the like.

The heterocyclic compounds (I) and a pharmaceutically acceptable salt thereof scarcely have side effect exerting a bad influence upon patients.

In order to show the utilities of the heterocyclic compounds (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the heterocyclic compounds (I) are illustrated in the following.

The expressions of "Example 1-(1)", "Example 2-(1)" and "Example 7-(3)" "Example 17-(2)", "Example 21-(1)" and "Example 24-(1)" in the following tests mean the compounds prepared in Example 1-(1), 2-(1), 7-(3), 17-(2), 21-(1) and 24-(1) respectively.

Platelet aggregation ex vivo

1. Test method

Male Hartley guinea-pigs weighing about 300 g were used after 24 hours fasting. Six hours after oral administration of the test compound or vehicle of test compound (control), blood was collected into a tube containing 0.1 vol. of 3.8% sodium citrate and platelet rich plasma (PRP) was prepared.

To the 250 μ l of PRP, 5 μ l of arachidonic acid (final 50 μ M) was added as an aggregation inducer. Aggregation was measured by using an aggregometer (NKK HEMA-TRACER 1). The following result shows the relationship between the dose of the test compound and the percentage (%) of its inhibitory activity against the platelet aggregation responses.

2. Test result

Test compound	Dose (mg/kg)	Inhibition (%)
Example 2-(1)	1.0	100
Example 21-(1)	1.0	68.3

Relaxation effect on isolated rat aorta

1. Test method

Helical strip of rat thoracic aorta was suspended in the organ bath containing Tyrode solution gassed with 95% O_2 - 5% CO_2 at 37°C under 0.5 g load. Contraction was induced by addition of KCl solution (final concentration was 30 mM). After the tonus reached plateau, drug solution (dissolved in dimethyl sulfoxide) was added cumulatively and finally 10^{-4} M of papaverine was added to get maximum relaxation. Activities of the test compound were

expressed as ED₅₀ values i.e. doses required to relax the isolated rat aorta by 50%.

2. Test result

5

Test compounds	ED ₅₀ (M)
Example 1-(1)	4.3 x 10 ⁻⁵
Example 2-(1)	4.5 x 10 ⁻⁵
Example 24-(1)	4.6 x 10 ⁻⁶

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Effect on malondialdehyde (MDA) production in rabbit platelets

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1. Test method

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Washed rabbit PRP (990 µl) was preincubated with drug solution (dissolved in dimethyl sulfoxide) (10 µl) at 37°C for 5 minutes. Then, 2.5 mM arachidonic acid solution (20 µl) was added to the reaction mixture. After 3 minutes, thiobarbiturate reagent (1000 µl) was added, and the reaction mixture was heated in a boiled water for 10 minutes. After centrifugation at 1500 g for 10 minutes, the absorbance of suparnatant was measured at 532 nm. This test was carried out to see inhibitory activity of the test compound against the activity of cyclooxygenase.

30

2. Test result

35

Test compound	concentration (M)	Inhibition (%)
Example 7-(3)	1.0 x 10 ⁻⁷	73.5
Example 17-(2)	1.0 x 10 ⁻⁷	80.1

For therapeutic administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration.

5 The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution,

10 suspension or emulsion for injection, ingestion, eye drops, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

15

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

20

The following preparations and examples are given only for the purpose of illustrating the present invention in more detail.

25

Preparation 1

To a solution of anisil (25 g) and sodium hydroxide (21.62 g) in methanol (1.5 l) was added 2,3-diaminopropanoic acid hydrobromide (36.52 g). The mixture was refluxed for 1 hour, and the cooled mixture was filtered. The filtrate was concentrated to a volume of 200 ml under reduced pressure and insolble material was collected by filtration. A mixture of this precipitate, water (100 ml) and ethyl acetate (50 ml) was adjusted to pH 10.5 with 3N-sodium hydroxide aqueous solution and the resultant mixture was acidified to pH 4.0 with 4N-hydrochloric acid. The precipitate was collected and washed with water to give 2,3-bis(4-methoxyphenyl)-pyrazine-5-carboxylic acid.

mp : 233°C (dec.)

IR (Nujol) : 1690, 1600, 1510 cm⁻¹

NMR (DMSO-d₆, δ) : 2.80 (6H, s), 6.97, 7.46 (8H, ABq, J=9Hz), 9.13 (1H, s)

MASS (m/z) : 336 (M⁺)

20

Preparation 2

A mixture of 2,3-bis(4-methoxyphenyl)pyrazine-5-carboxylic acid (0.5 g), 3-methyl-1-p-tolyltriazine (0.44 g) in tetrahydrofuran (15 ml) was stirred at 40°C for 1 hour. The reaction mixture was poured into a mixture of ethyl acetate and water and adjusted to pH ≈ 2 with 6N-hydrochloric acid. The separated organic layer was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo, and the resulting precipitate was washed with isopropyl ether to give 5-methoxycarbonyl-2,3-bis(4-methoxyphenyl)pyrazine (0.36 g).

IR (Nujol) : 1720, 1600, 1505 cm⁻¹

NMR (CDCl₃, δ) : 3.82 (3H, s), 3.83 (3H, s), 4.04 (3H, s), 6.85 (4H, d, J=9Hz), 7.47 (2H, d,

- 50 -

J=9Hz), 7.48 (2H, d, J=9Hz), 9.18 (1H, s)
Mass (m/z) : 350 (M⁺)

Example 1

5 (1) To a mixture of 2-acetylamino-1-thioxoethylamine (0.50 g) and ethanol was added hydrazine monohydrate (0.18 ml) at -70°C and the mixture was stirred at the same temperature for 30 minutes. To the reaction mixture containing 2-acetylamino-1-hydrazonoethylamine was added 10 p-anisil (1.02 g) at -20°C, and an ethanol solution of hydrogen chloride (3 drops) was added thereto. The reaction mixture was stirred and refluxed for 20 minutes. After allowing to cool to room temperature, the mixture was poured into water, and extracted with ethyl acetate.

15 The organic layer was washed with saturated aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate and treated with active carbon. After filtration, the filtrate was evaporated in vacuo, the residue was subjected to column chromatography on silica gel (50 g)

20 and eluted with a mixture of chloroform and methanol. The fractions containing the object compound were combined and evaporated in vacuo, and the residue was triturated with isopropyl ether to give 3-(acetylaminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (0.20 g).

25 mp : 44-55°C

IR (Nujol) : 1650, 1600, 1490 cm⁻¹

NMR (CDCl₃, δ) : 2.13 (3H, s), 3.83 (3H, s),
3.85 (3H, s), 4.90 (2H, d, J=5Hz),
6.8-7.1 (5H, m), 7.55 (2H, d, J=9Hz),

30 7.58 (2H, d, J=9Hz)

MASS (m/z) : 364 (M⁺)

The following compounds were obtained according to a similar manner to that of Example 1-(1).

- 51 -

- (2) 3-Ethoxycarbonyl-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

mp : 120-122°C

IR (Nujol) : 1740, 1650, 1595, 1570 cm⁻¹

NMR (CDCl₃, δ) : 1.50 (3H, t, J=7Hz), 3.84 (3H, s), 3.86 (3H, s), 4.6 (2H, q, J=7Hz), 6.88 (2H, d, J=9Hz), 6.96 (2H, d, J=9Hz), 7.62 (2H, d, J=9Hz), 7.69 (2H, d, J=9Hz)

MASS (m/z) : 365 (M⁺)

10

- (3) 3-(2-tert-Butyloxycarbonylaminoethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

mp : 102-105°C

IR (Nujol) : 3320, 1680, 1610, 1490, 1250 cm⁻¹

NMR (DMSO-d₆, δ) : 1.33 (9H, s), 3.18 (2H, t, J=6Hz), 3.48 (2H, q, J=6Hz), 3.78 (3H, s), 3.80 (3H, s), 6.95 (2H, d, J=9Hz), 6.99 (2H, d, J=9Hz), 7.43 (2H, d, J=9Hz), 7.52 (2H, d, J=9Hz)

MASS (m/z) : 436 (M⁺)

20

- (4) 3-(1-tert-Butyloxycarbonylamino-1-methylethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

mp : 140°C

IR (Nujol) : 3250, 1700, 1600, 1490, 1300, 1250 cm⁻¹

NMR (DMSO-d₆, δ) : 1.31 (9H, s), 1.68 (6H, s), 3.79 (3H, s), 3.80 (3H, s), 6.97 (2H, d, J=9Hz), 7.01 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.51 (2H, d, J=9Hz)

MASS (m/z) : 450 (M⁺)

30

- (5) 3-(N,N-Dimethylaminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

IR (Neat) : 2820, 1600, 1480, 1250 cm⁻¹

NMR (DMSO-d₆, δ) : 2.33 (6H, s), 3.79 (3H, s), 3.80 (3H, s), 3.87 (2H, s), 6.95 (2H, d, J=8Hz), 6.99

- 52 -

(2H, d, J=8Hz), 7.45 (2H, d, J=8Hz), 7.52 (2H,
d, J=8Hz)

MASS (m/z) : 350 (M^+)

5 (6) 5,6-Bis(4-methoxyphenyl)-3-{(4-methylpiperazin-1-yl)-
carbonyl}-1,2,4-triazine hydrochloride
mp : 252-254°C
IR (Nujol) : 3400, 2400, 1645, 1600, 1575 cm^{-1}

10 Example 2

(1) A mixture of 3-ethoxycarbonyl-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (1.00g) and N-methylpiperazine (1.82 ml) was heated at 80-90°C for 4 hours and 40 minutes. After allowing to cool to room temperature, the mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and treated with active carbon. After filtration, the filtrate was evaporated in vacuo, and the resulting matter was dissolved with diethyl ether, and to it was added an ethanol solution of hydrogen chloride. The resulting precipitate was collected by filtration, washed with ethanol and diethyl ether, and dried to give 5,6-bis(4-methoxyphenyl)-3-{(4-methylpiperazin-1-yl)-carbonyl}-1,2,4-triazine hydrochloride (0.76 g).

20 mp : 252-254°C
IR (Nujol) : 3400, 2400, 1645, 1600, 1575 cm^{-1}
NMR (DMSO-d₆, δ) : 2.81 (3H, s), 2.80-4.80 (8H, m),
3.80 (3H, s), 3.81 (3H, s), 6.98 (2H, d, J=9Hz),
7.03 (2H, d, J=9Hz), 7.53 (4H, d, J=9Hz)
25 MASS (m/z) : 418 [M^+ (419) of free compound-1]

30 The following compounds were obtained according to a similar manner to that of Example 2-(1).

- (2) 3-[(4-(2-Hydroxyethyl)piperazin-1-yl)carbonyl]-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride
mp : 141-147°C
IR (Nujol) : 1650, 1610 cm⁻¹
5 NMR (DMSO-d₆, δ) : 2.8-4.8 (12H, m), 3.80 (3H, s),
3.81 (3H, s), 6.98 (2H, d, J=9Hz),
7.03 (2H, d, J=9Hz), 7.53 (4H, d, J=9Hz)
MASS (m/z) : 449 (M⁺ of free compound)
- 10 (3) 3-(Morpholinocarbonyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
mp : 65-70°C
IR (Nujol) : 1650, 1600, 1580 cm⁻¹
NMR (DMSO-d₆, δ) : 3.4-3.8 (8H, m), 3.79 (3H, s),
15 3.81 (3H, s), 6.96 (2H, d, J=9Hz),
7.03 (2H, d, J=9Hz), 7.53 (4H, d, J=9Hz)
MASS (m/z) : 406 (M⁺)
- 20 (4) 3-(N,N-Dimethylaminocarbonyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
mp : 50-60°C
IR (Nujol) : 1650, 1600 cm⁻¹
NMR (DMSO-d₆, δ) : 2.98 (3H, s), 3.10 (3H, s),
3.79 (3H, s), 3.81 (3H, s), 6.96 (2H, d, J=9Hz),
25 7.01 (2H, d, J=9Hz), 7.53 (4H, d, J=9Hz)
MASS (m/z) : 364 (M⁺)
- 30 (5) 3-[(2-(N,N-Dimethylamino)ethyl]carbamoyl]-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
mp : 137-140°C
IR (Nujol) : 1690, 1600, 1250 cm⁻¹
NMR (DMSO-d₆, δ) : 2.21 (6H, s), 2.48 (2H, t,
J=6Hz), 3.46 (2H, q, J=6Hz), 3.80 (3H, s), 3.81
35 (3H, s), 6.98 (2H, d, J=8Hz), 7.02 (2H, d,
J=8Hz), 7.53 (2H, d, J=8Hz), 7.61 (2H, d,

- 54 -

J=8Hz), 9.06 (1H, t, J=6Hz)

MASS (m/z) : 407 (M⁺)

- (6) 3-[(4-Benzylpiperazin-1-yl)carbonyl]-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

5 mp : 126-129°C

IR (Nujol) : 1630, 1600, 1480 cm⁻¹

10 NMR (CDCl₃, δ) : 2.4-2.7 (4H, m), 3.57 (2H, s),
3.7-4.0 (4H, m), 3.83 (3H, s), 3.85 (3H, s),
6.84 (2H, d, J=8.9Hz), 6.92 (2H, d, J=8.9Hz),
7.2-7.45 (5H, m), 7.56 (2H, d, J=8.9Hz), 7.66
(2H, d, J=8.9Hz)

- (7) 3-[(1-Benzylpiperidin-4-yl)carbamoyl]-5,6-bis(4-methoxyphenyl)-1,2,4-triazine

15 mp : 132-136°C

IR (Nujol) : 3380, 1690, 1600, 1520, 1490 cm⁻¹

20 NMR (CDCl₃, δ) : 1.55-2.4 (6H, m), 2.75-3.0 (2H, m),
3.54 (2H, s), 3.84 (3H, s), 3.86 (3H, s),
4.03-4.18 (1H, m), 6.86 (2H, d, J=8.9Hz), 6.93
(2H, d, J=8.9Hz), 7.18-7.5 (5H, m), 7.59 (2H, d,
J=8.9Hz), 7.69 (2H, d, J=8.9Hz), 8.01 (1H, d,
J=8.2Hz)

25 MASS (m/z) : 509 (M⁺)

Example 3

A mixture of 3-(acetylaminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (0.79 g) and concentrated hydrochloric acid (5 ml) was stirred and refluxed for 2 hours. After allowing to cool to room temperature, the mixture was poured into water. Then, an aqueous solution of sodium bicarbonate was added thereto to adjust to pH 10, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and treated with active carbon. After filtration,

the filtrate was evaporated in vacuo, and the resulting matter was dissolved with ethanol and to it was added an ethanol solution of hydrogen chloride. To the resulting mixture was added diethyl ether and it was triturated to give powder of 3-(aminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (0.18 g).

5 mp : 163-173°C (decomp.)
IR (Nujol) : 1600, 1580, 1520 cm⁻¹
10 NMR (DMSO-d₆, δ) : 3.80 (3H, s), 3.81 (3H, s),
4.52 (2H, br s), 6.98 (2H, d, J=9Hz),
7.03 (2H, d, J=9Hz), 7.49 (2H, d, J=9Hz),
7.63 (2H, d, J=9Hz), 9.00 (3H, br s)
MASS (m/z) : 322 (M⁺ of free compound)

15 Example 4

A mixture of 3-(aminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (1.00 g), chloroform and an aqueous solution of sodium bicarbonate was stirred at ambient temperature for 30 minutes, and the separated organic layer was dried over magnesium sulfate and treated with active carbon. After filtration, the filtrate was evaporated in vacuo. The resulting matter was dissolved with N,N-dimethylformamide (10 ml), and to the mixture were added 6-carboxyl-3-oxo-2,3,4,5-tetrahydropyridazine (0.40 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) and triethylamine (0.39 ml). The resulting mixture was stirred at 100°C for 15 hours. After allowing to cool to room temperature, the mixture was poured into water, and extracted with ethyl acetate. The separated organic layer was washed with water, diluted aqueous hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, water and brine, dried over magnesium sulfate and treated with active carbon. After filtration, the filtrate was evaporated in vacuo, the residue was

- 56 -

subjected to column chromatography on silica gel (25 g) and eluted with a mixture of chloroform and methanol. The fractions containing the object compound were combined and evaporated in vacuo, and the residue was triturated with ethanol and diethyl ether to give
5 5,6-bis(4-methoxyphenyl)-3-{(3-oxo-2,3,4,5-tetrahydro-pyridazin-6-yl)carbonylaminomethyl}-1,2,4-triazine (0.07 g).

mp : 183-187°C
10 IR (Nujol) : 3400, 1700, 1670, 1660, 1640, 1610,
1580 cm^{-1}
NMR (DMSO-d₆, δ) : 2.47 (2H, t, J=8.2Hz), 2.78 (2H, t, J=8.2Hz), 3.78 (3H, s), 3.80 (3H, s), 4.78 (2H, d, J=5.8Hz), 6.95 (2H, d, J=8.3Hz),
15 7.00 (2H, d, J=8.3Hz), 7.45 (2H, d, J=8.3Hz), 7.49 (2H, d, J=8.3Hz), 8.75 (1H, t, J=5.8Hz)
MASS (m/z) : 446 (M⁺)

Example 5

20 (1) A mixture of 5,6-bis(4-methoxyphenyl)-3-[2-(tert-butylloxycarbonylamino)ethyl]-1,2,4-triazine (1.00 g) and dichloromethane (10 ml) was stirred at 2°C. To the reaction mixture was added 4N-hydrogen
chloride-1,4-dioxane (10 ml), and the mixture was stirred at ambient temperature for 1 hour. The resulting matter was evaporated in vacuo. To the residue was added isopropyl ether (50 ml) and it was stirred at 2°C for 3 hours. The resulting precipitate was collected by filtration and washed with isopropyl ether to give
30 3-(2-aminoethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (0.73 g).

mp : 98°C (decomp.)
IR (Nujol) : 3500-3300, 1600, 1510, 1310, 1260 cm^{-1}
NMR (DMSO-d₆, δ) : 3.17-3.70 (4H, m), 3.79 (3H, s),
35 3.80 (3H, s), 6.97 (3H, d, J=9Hz),

- 57 -

7.01 (3H, d, J=9Hz), 7.46 (3H, d, J=9Hz),
7.53 (3H, d, J=9Hz), 8.01 (2H, br s)

MASS : m/z 336 (M^+ of free compound)

5 The following compound was obtained according to a similar manner to that of Example 5-(1).

(2) 3-(1-Amino-1-methylethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride

10 mp : 245-247°C

IR (Nujol) : 3600-3300, 1600, 1490, 1300 cm^{-1}

NMR (DMSO-d₆, δ) : 1.79 (6H, s), 3.80 (3H, s),
3.81 (3H, s), 6.99 (2H, d, J=9Hz),
7.03 (2H, d, J=9Hz), 7.50 (2H, d, J=9Hz),
7.65 (2H, d, J=9Hz), 8.93 (3H, br s)

15 MASS (m/z) : 350 (M^+)

Example 6

(1) To a solution of 3-(1-amino-1-methylethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (1.30 g), 3-oxo-6-carboxy-2,3,4,5-tetrahydropyridazine (0.48 g) and 1-hydroxybenzotriazole hydrate (0.52 g) in N,N-dimethylformamide (30 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.62 ml) under stirring at ambient temperature and the resulting mixture was stirred for one hour at same condition. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, water and brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo. The resulting precipitate was collected by filtration, and washed with diethyl ether to give 5,6-bis(4-methoxyphenyl)-3-[1-{(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)carbonylamino}-1-methylethyl]-1,2,4-triazine (1.33 g).

- 58 -

mp : 221-222°C

IR (Nujol) : 3350, 3250, 1700, 1660, 1600, 1500,
1250 cm⁻¹

NMR (DMSO-d₆, δ) : 1.83 (6H, s), 2.42 (2H, t, J=8Hz),
2.72 (2H, t, J=8Hz), 3.79 (3H, s), 3.80 (3H, s),
6.97 (2H, d, J=9Hz), 7.02 (2H, d, J=9Hz),
7.48 (2H, d, J=9Hz), 7.53 (2H, d, J=9Hz),
8.72 (1H, s), 11.20 (1H, s)

MASS (m/z) : 474 (M⁺)

10

The following compound was obtained according to a similar manner to that of Example 6-(1).

(2) 5,6-Bis(4-methoxyphenyl)-3-[2-{(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)carbonylamino}ethyl]-1,2,4-triazine

mp : 85°C (decomp.)

IR (Nujol) : 3500-3200, 1660, 1600, 1250 cm⁻¹

NMR (DMSO-d₆, δ) : 2.36 (2H, t, J=8Hz),
2.70 (2H, t, J=8Hz), 3.30-3.36 (2H, m),
3.78 (3H, s), 3.80 (3H, s), 6.91 (2H, d, J=9Hz),
7.00 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz),
7.50 (2H, d, J=9Hz), 8.33 (1H, t, J=6Hz),
11.10 (1H, s)

MASS (m/z) : 460 (M⁺)

20

25

Example 7

(1) A mixture of 3-(aminomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (0.80 g), chloroform and an aqueous solution of sodium bicarbonate was stirred at ambient temperature for 30 minutes, and the separated organic layer was dried over magnesium sulfate and treated with active carbon. After filtration, the filtrate was evaporated in vacuo. To the resulting matter was added a mixture of tetrahydrofuran

30

35

(20 ml) and methanol (7 ml), and to the mixture was added isopropyl isocyanate (0.26 ml). The reaction mixture was stirred at ambient temperature for 3 hours and 50 minutes. The mixture was evaporated in vacuo, and the resulting matter was triturated with isopropyl ether and diethyl ether to give 3-(N'-isopropylureidomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (0.75 g).

mp : 80-83°C
IR (Nujol) : 3300, 1630, 1600, 1560, 1490 cm⁻¹
NMR (DMSO-d₆, δ) : 1.06 (6H, d, J=6.5Hz),
3.70 (1H, m), 3.78 (3H, s), 3.80 (3H, s),
4.64 (2H, d, J=5.8Hz), 6.14 (1H, d, J=7.7Hz),
6.45 (1H, t, J=5.8Hz), 6.95 (2H, d, J=8.8Hz),
7.00 (2H, d, J=8.8Hz), 7.45 (2H, d, J=8.8Hz),
7.52 (2H, d, J=8.8Hz)
MASS (m/z) : 407 (M⁺)

The following compounds were obtained according to a similar manner to that of Example 7-(1).

(2) 3-(N'-Ethylureidomethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
mp : 69-74°C
IR (Nujol) : 3300, 1640, 1600, 1560 cm⁻¹
NMR (DMSO-d₆, δ) : 1.03 (3H, t, J=7Hz),
3.05 (2H, q, J=7Hz), 3.78 (3H, s), 3.80 (3H, s),
4.64 (2H, d, J=5.9Hz), 6.23 (1H, t, J=5.5Hz),
6.56 (1H, t, J=5.5Hz), 6.95 (2H, d, J=9Hz),
7.00 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz),
7.52 (2H, d, J=9Hz)
MASS (m/z) : 393 (M⁺)

(3) 3-[2-(N'-Isopropylureido)ethyl]-5,6-bis(4-methoxyphenyl)-1,2,4-triazine
mp : 157-160°C

- 60 -

IR (Nujol) : 3400-3200, 1640, 1620, 1570, 1180 cm⁻¹
NMR (DMSO-d₆, δ) : 0.98 (6H, d, J=6.5Hz), 3.20 (2H,
5 t, J=7Hz), 3.51-3.72 (3H, m), 3.79 (3H, s),
3.80 (3H, s), 5.73 (1H, d, J=7.5Hz),
5.85 (1H, t, J=6Hz), 6.96 (2H, d, J=9Hz),
6.99 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz),
7.52 (2H, d, J=9Hz)
MASS (m/z) : 421 (M⁺)

10 Example 8

(1) A solution of 5,6-bis(4-methoxyphenyl)-3-(pyridin-4-yl)-1,2,4-triazine (0.50 g) and methyl iodide (0.75 ml) in a mixture of chloroform and methanol (9:1) (20 ml) was allowed to stand at ambient temperature for 1 day. The reaction mixture containing 4-[5,6-bis(4-methoxyphenyl)-triazin-3-yl]-1-methylpyridinium iodide was evaporated in vacuo and the residue was dissolved in a mixture of methanol (30 ml) and water (10 ml). To the resultant solution was added portionwise sodium borohydride (0.10 g) under stirring at 5 to 10°C. The reaction mixture was stirred for 2.5 hours at the same temperature. Water (100 ml) was added to the reaction mixture and the resulting precipitate was collected by filtration. The precipitate was dissolved in chloroform, washed with brine and dried over magnesium sulfate. The separated organic layer was evaporated in vacuo, and the residue was washed with diethyl ether to give 5,6-bis(4-methoxyphenyl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1,2,4-triazine (0.32 g).

30 mp : 163-165°C

IR (Nujol) : 1600, 1300, 1250 cm⁻¹
NMR (DMSO-d₆, δ) : 2.33 (3H, s), 2.64 (2H, m),
35 2.76 (2H, m), 3.17 (2H, m), 3.78 (3H, s),
3.80 (3H, s), 6.95 (2H, d, J=9Hz),
7.00 (2H, d, J=9Hz), 7.33 (1H, m),

- 61 -

7.47 (2H, d, J=9Hz), 7.54 (2H, d, J=9Hz)
MASS (m/z) : 388 (M⁺)

5 The following compound was obtained according to a
similar manner to that of Example 8-(1).

(2) 5,6-Bis(4-methoxyphenyl)-3-[1-(4-fluorobenzyl)-
1,2,3,6-tetrahydropyridin-4-yl]-1,2,4-triazine
mp : 137-138°C
10 IR (Nujol) : 1645, 1600, 1570, 1505 cm⁻¹
NMR (DMSO-d₆, δ) : 2.70 (4H, br s), 3.21 (2H, br s),
3.63 (2H, s), 3.78 (3H, s), 3.79 (3H, s),
6.91-7.00 (4H, m), 7.12-7.20 (2H, m),
7.20-7.55 (7H, m)
15 MASS (m/z) : 482 (M⁺)

Example 9

(1) A mixture of 3-ethoxycarbonyl-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (10 g) and 2,5-norbornadiene (5.55 g) in the xylene (400 ml) was refluxed under stirring for 24 hours. The reaction mixture was evaporated in vacuo, and the resulting precipitate was washed with diethyl ether to give
25 6-ethoxycarbonyl-2,3-bis(4-methoxyphenyl)pyridine (6.47 g).

mp : 108-109°C
IR (Nujol) : 1700, 1600, 1505 cm⁻¹
NMR (CDCl₃, δ) : 1.45 (3H, t, J=7Hz), 3.79 (3H, s),
3.81 (3H, s), 4.48 (2H, q, J=7Hz), 6.78 (2H, d,
30 J=8Hz), 6.84 (2H, d, J=8Hz), 7.12 (2H, d,
J=8Hz), 7.37 (2H, d, J=8Hz), 7.78 (1H, d,
J=8Hz), 8.05 (1H, d, J=8Hz)
MASS (m/z) : 363 (M⁺)

35 The following compounds were obtained according to a

- 62 -

similar manner to that of Example 9-(1).

(2) 6-Acetylaminomethyl-2,3-bis(4-methoxyphenyl)pyridine

IR (Film) : 1720 cm^{-1}

NMR (CDCl_3 , δ) : 2.08 (3H, s), 3.80 (3H, s),
3.81 (3H, s), 4.63 (2H, d, $J=5\text{Hz}$),
6.7-7.0 (5H, m), 7.07 (2H, d, $J=8\text{Hz}$),
7.2-7.4 (3H, m), 7.64 (1H, d, $J=8\text{Hz}$)

MASS (m/z) : 362 (M^+)

10

(3) 6-(Pyridin-4-yl)-2,3-bis(4-methoxyphenyl)pyridine

mp : 175-178°C

IR (Nujol) : 1610, 1600, 1510, 1250 cm^{-1}

15

NMR (DMSO-d_6 , δ) : 3.77 (6H, s), 6.90 (2H, d, $J=8\text{Hz}$),
6.94 (2H, d, $J=8\text{Hz}$), 7.19 (2H, d, $J=8\text{Hz}$),
7.37 (2H, d, $J=8\text{Hz}$), 7.93 (1H, br s),
8.15 (1H, br s), 8.74 (2H, br s)

MASS (m/z) : 368 (M^+)

20

(4) 2,3-Bis(4-methoxyphenyl)-6-(N,N-dimethylaminomethyl)-pyridine

mp : 103-108°C (dec.)

IR (Nujol) : 1610, 1510, 1250 cm^{-1}

25

NMR (DMSO-d_6 , δ) : 2.82 (3H, s), 2.83 (3H, s), 3.74
(3H, s), 3.76 (3H, s), 4.46 (2H, s), 6.84 (2H,
d, $J=8\text{Hz}$), 6.90 (2H, d, $J=8\text{Hz}$), 7.13 (2H,
 $J=8\text{Hz}$), 7.32 (2H, d, $J=8\text{Hz}$), 7.63 (1H, d,
 $J=8\text{Hz}$), 7.85 (2H, d, $J=8\text{Hz}$)

30

Example 10

(1) A mixture of 6-ethoxycarbonyl-2,3-bis(4-methoxyphenyl)pyridine (1.03 g) and N-methylpiperazine (1.87 ml) was stirred and refluxed for 26.5 hours. After allowing to cool to room temperature, the reaction mixture was poured into water and ethyl

acetate. The separated organic layer was washed with water, saturated aqueous sodium bicarbonate, water and brine, and dried over magnesium sulfate and treated with active carbon.

5 After filtration, the filtrate was evaporated in vacuo, and the resulting residue was dissolved with diethyl ether, and to it was added an ethanol solution of hydrogen chloride. The resulting precipitate was collected by filtration and washed with ethanol and
10 diethyl ether to give 2,3-bis(4-methoxyphenyl)-6-[(4-methyl-piperazin-1-yl)carbonyl]pyridine dihydrochloride (0.25 g).

mp : 213-216°C

15 IR (Nujol) : 3400 (br), 2400 (br), 1980 (br),
1650, 1610, 1510 cm^{-1}

NMR (DMSO-d₆, δ) : 2.77 (3H, s), 2.8-4.8 (8H, m),
3.75 (3H, s), 3.76 (3H, s), 6.85 (2H, d, J=9Hz),
6.91 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz),
7.26 (2H, d, J=9Hz), 7.68 (1H, d, J=9Hz),
20 7.92 (1H, d, J=9Hz)

MASS (m/z) : 415 [M⁺(417) of free compound -2]

The following compounds were obtained according to a similar manner to that of Example 10-(1).

25

(2) 2,3-Bis(4-methoxyphenyl)-6-[(2-(N,N-dimethylamino)-ethyl)carbamoyl]pyridine dihydrochloride

mp : 68-71°C

IR (Nujol) : 1600, 1510, 1300, 1250 cm^{-1}
30 NMR (DMSO-d₆, δ) : 2.80 (3H, s), 2.83 (3H, s),
3.28 (2H, q, J=6Hz), 3.73 (2H, t, J=6Hz),
3.75 (3H, s), 3.76 (3H, s), 6.86 (2H, d, J=8Hz),
6.91 (2H, d, J=8Hz), 7.15 (2H, d, J=8Hz),
7.42 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz),
35 8.00 (2H, d, J=8Hz), 9.02 (1H, t, J=6Hz),

- 64 -

10.58 (1H, m)

MASS (m/z) : 405 (M^+ of free compound)

(3) 2,3-Bis(4-methoxyphenyl)-6-[(4-benzylpiperazin-1-yl)-
5 carbamoyl]pyridine

mp : 126-132°C

IR (Nujol) : 1610, 1500 cm^{-1}

NMR (CDCl_3 , δ) : 2.4-2.7 (4H, m), 3.56 (2H, s),
10 3.7-3.95 (4H, m), 3.79 (3H, s), 3.81 (3H, s),
6.77 (2H, d, $J=8.9\text{Hz}$), 6.83 (2H, d, $J=8.9\text{Hz}$),
7.11 (2H, d, $J=8.9\text{Hz}$), 7.2-7.45 (7H, m),
7.63 (1H, d, $J=7.9\text{Hz}$), 7.75 (1H, d, $J=7.9\text{Hz}$)

MASS (m/z) : 493 (M^+)

15 Example 11

(1) To a mixture of lithium aluminum hydride (0.24 g) and tetrahydrofuran (20 ml) was added a solution of 6-ethoxycarbonyl-2,3-bis(4-methoxyphenyl)pyridine (2.1 g) in tetrahydrofuran (2.1 ml) with stirring and ice-cooling, and the mixture was stirred for 1 hour at the same temperature. To the reaction mixture were added ethyl acetate (20 ml) and water (20 ml) very carefully. The organic layer was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo to give 6-hydroxymethyl-2,3-bis(4-methoxyphenyl)pyridine (2.04 g).

NMR (CDCl_3 , δ) : 3.79 (3H, s), 3.81 (3H, s),
4.82 (2H, s), 6.79 (2H, d, $J=9\text{Hz}$),
6.84 (2H, d, $J=9\text{Hz}$), 7.0-7.4 (5H, m),

30 7.67 (1H, d, $J=8\text{Hz}$)

Mass (m/z) : 321 (M^+)

(2) A mixture of 6-hydroxymethyl-2,3-bis(4-methoxyphenyl)pyridine (2 g) and activated manganese dioxide (6 g) in the chloroform (20 ml) was

- 65 -

stirred at ambient temperature for 5.5 hours. After filtration, the filtrate was evaporated in vacuo, and the resulting precipitate was washed with isopropyl ether to give 2,3-bis(4-methoxyphenyl)-6-pyridinecarbaldehyde (1.61 g).

MMR (CDCl_3 , δ) : 3.81 (3H, s), 3.82 (3H, s),
6.81 (2H, d, $J=9\text{Hz}$), 6.84 (2H, d, $J=9\text{Hz}$),
7.12 (2H, d, $J=9\text{Hz}$), 7.37 (2H, d, $J=9\text{Hz}$),
7.81 (1H, d, $J=8\text{Hz}$), 7.95 (1H, d, $J=8\text{Hz}$)

MASS (m/z) : 319 (M^+)

Example 12

The following compound was obtained by reacting 5-methoxycarbonyl-2,3-bis(4-methoxyphenyl)pyrazine according to a similar manner to that of Example 11.

2,3-Bis(4-methoxyphenyl)-6-pyrazinecarbaldehyde
IR (Nujol) : 1700, 1600, 1505 cm^{-1}
NMR (CDCl_3 , δ) : 3.83 (3H, s), 3.84 (3H, s),
6.8-7.0 (4H, m), 7.44-7.6 (4H, m),
9.07 (1H, s), 10.22 (1H, s)
MASS (m/z) : 320 (M^+)

Example 13

(1) A mixture of 2,3-bis(4-methoxyphenyl)-6-pyridinecarbaldehyde (0.6 g), malonic acid (0.98 g), piperidine (0.1 ml) and pyridine (6 ml) was refluxed under stirring for 1 hour and 20 minutes. After allowing to cool to room temperature, the mixture was poured into water and ethyl acetate, and adjusted to pH =10.5 with an aqueous solution of 4N sodium hydroxide. The separated aqueous layer was washed with ethyl acetate, and the aqueous layer was adjusted to pH ≈4 with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate.

- 66 -

After filtration, the filtrate was evaporated in vacuo to give 3-[2,3-bis(4-methoxyphenyl)pyridin-6-yl]-(E)-propenoic acid (0.35 g).

5 mp : 160-170°C
IR (Nujol) : 1680, 1630, 1600, 1500 cm⁻¹
NMR (DMSO-d₆, δ) : 3.75 (6H, s), 6.75-6.97 (4H, m),
6.85 (1H, d, J=15.6Hz), 6.99-7.35 (4H, m),
7.67 (1H, d, J=16Hz), 7.69 (1H, d, J=8Hz),
7.8 (1H, d, J=8Hz)
10 MASS (m/z) : 361 (M⁺)

The following compound was obtained according to a similar manner to that of Example 13-(1).

15 (2) 3-[2,3-Bis(4-methoxyphenyl)pyrazin-5-yl]-(E)-
propenoic acid
mp : 238-240°C
IR (Nujol) : 1680, 1630, 1600, 1500 cm⁻¹
NMR (CDCl₃ + DMSO-d₆, δ) : 3.82 (3H, s), 3.83 (3H,
20 s),
6.85-6.93 (4H, m), 7.07 (1H, d, J=15.6Hz),
7.35-7.54 (4H, m), 7.75 (1H, d, J=15.6Hz),
8.56 (1H, s)
MASS (m/z) : 362 (M⁺)

25 Example 14
(1) A mixture of 3-[2,3-bis(4-methoxyphenyl)pyridin-6-yl]-(E)-propenoic acid (0.8 g) and 10% palladium-carbon (0.16 g) in methanol (8 ml) was stirred under hydrogen at low pressure at ambient temperature for 5 hours. The insoluble material was filtered and washed with a mixture of chloroform and methanol, and the filtrate was evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate and water and the resultant solution was adjusted to pH ≈ 4 with 6N-hydrochloric acid. The organic layer was washed with brine and dried over

magnesium sulfate. The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol (10:1). The eluted solution was evaporated in vacuo and the resulting precipitate was washed with diethyl ether to give 3-[2,3-bis(4-methoxyphenyl)pyridin-6-yl]propanoic acid (495 mg).

5 mp : 146-147°C
IR (Nujol) : 1710, 1600, 1510 cm⁻¹
10 NMR (CDCl₃, δ) : 2.8-2.95 (2H, m), 3.15-3.29 (2H, m),
3.8 (3H, s), 3.81 (3H, s), 6.75-7.33 (9H, m),
7.76 (1H, d, J=8Hz)
MASS (m/z) : 363 (M⁺)

15 The following compound was obtained according to a similar manner to that of Example 14-(1).

(2) 3-[2,3-Bis(4-methoxyphenyl)pyrazin-5-yl]propanoic acid
20 mp : 120-128°C
IR (Nujol) : 1700, 1600, 1570, 1500 cm⁻¹
NMR (CDCl₃, δ) : 2.8-3.0 (2H, m), 3.1-3.3 (2H, m),
3.8 (3H, s), 3.81 (3H, s), 6.83 (2H, d, J=9Hz),
6.84 (2H, d, J=9Hz), 7.37 (2H, d, J=9Hz),
25 7.38 (2H, d, J=9Hz), 8.46 (1H, s)
MASS (m/z) : 364 (M⁺)

Example 15

(1) A mixture of 6-acetylaminomethyl-2,3-bis(4-methoxyphenyl)pyridine (1.64 g) and concentrated hydrochloric acid (3.3 ml) was stirred and refluxed for 1.5 hours. The reaction mixture was poured into a mixture of ethyl acetate and ice-water and adjusted to pH =10 with 4N-sodium hydroxide. The separated organic layer was washed with brine and dried over magnesium sulfate. After

filtration, the filtrate was evaporated in vacuo, and the resulting residue was dissolved in ethanol and to it was added an ethanol solution of hydrogen chloride. To the resulting mixture was added diethyl ether and it was 5 triturated to give 6-aminomethyl-2,3-bis(4-methoxyphenyl)pyridine dihydrochloride (1.13 g).

mp : 150°C (dec.)
IR (Nujol) : 3400 (br), 1600, 1500 cm^{-1}
NMR (CDCl_3 , δ) : 3.71 (3H, s), 3.76 (3H, s),
10 5.2 (2H, br s), 6.75 (2H, d, $J=9\text{Hz}$),
6.81 (2H, d, $J=9\text{Hz}$), 7.01 (2H, d, $J=9\text{Hz}$),
7.45 (2H, d, $J=9\text{Hz}$), 8.31 (1H, d, $J=8\text{Hz}$),
8.54 (1H, d, $J=8\text{Hz}$), 9.49 (2H, br s)
MASS (m/z) : 320 (M^+ of free compound)

15 The following compound was obtained according to a similar manner to that of Example 15-(1).

(2) 2-Aminomethyl-4,5-bis(4-methoxyphenyl)pyrimidine
20 hydrochloride
IR (Nujol) : 1605, 1585, 1570, 1510 cm^{-1}
NMR (DMSO-d_6 , δ) : 3.78 (6H, s),
4.33 (2H, d, $J=6\text{Hz}$), 4.82 (2H, s),
25 6.90 (2H, d, $J=9\text{Hz}$), 6.98 (2H, d, $J=9\text{Hz}$),
7.21 (2H, d, $J=9\text{Hz}$), 7.50 (2H, d, $J=9\text{Hz}$),
8.76 (1H, s)

Example 16

(1) A mixture of 6-aminomethyl-2,3-bis(4-methoxyphenyl)-
30 pyridine dihydrochloride (0.2 g), 6-carboxy-3-oxo-2,3,4,5-tetrahydropyridazine (72 mg), N-hydroxybenzotriazole (69 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (97 mg) and triethylamine (0.15 g) in tetrahydrofuran (4 ml) was stirred at ambient temperature 35 for 15 hours. The reaction mixture was poured into water

- 69 -

and the resulting precipitate was washed with water and tetrahydrofuran to give 2,3-bis(4-methoxyphenyl)-6-[(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)- carbonylaminomethyl]pyridine (126 mg).

5 mp : 234-235°C
IR (Nujol) : 3380, 1670, 1655, 1620, 1500 cm⁻¹
NMR (CDCl₃, δ) : 2.55 (2H, t, J=8Hz),
2.98 (2H, t, J=8Hz), 3.80 (3H, s), 3.81 (3H, s),
4.70 (2H, d, J=5Hz), 6.73-6.87 (4H, m),
10 7.08 (2H, d, J=9Hz), 7.2-7.36 (4H, m),
7.64 (1H, d, J=8Hz), 8.1 (1H, br s),
8.63 (1H, s)
MASS (m/z) : 444 (M⁺)

15 The following compound was obtained according to a similar manner to that of Example 16-(1)

(2) 2,3-Bis-(4-methoxyphenyl)-6-[2-[(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)carbonylamino]ethyl]pyridine
20 mp : 148-151°C
IR (Nujol) : 1685, 1650, 1600, 1510, 1240 cm⁻¹
NMR (DMSO-d₆, δ) : 2.38 (2H, t, J=8Hz), 2.73 (2H, t, J=8Hz), 3.00 (2H, t, J=6Hz), 3.58 (2H, q, J=6Hz), 3.73 (3H, s), 3.74 (3H, s), 6.82 (2H, d, J=8Hz), 6.87 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.24 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.26 (1H, t, J=6Hz), 11.09 (1H, s)
MASS (m/z) : 458 (M⁺)

30 Example 17
(1) A mixture of 6-aminomethyl-2,3-bis(4-methoxyphenyl)-pyridine dihydrochloride (0.3 g), dichloromethane and an aqueous solution of sodium hydrogencarbonate was stirred at ambient temperature for 30 minutes, and the separated

- 70 -

organic layer was dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo. To the resulting residue was added a mixture of tetrahydrofuran (6 ml) and methanol (2 ml), and then added isopropyl isocyanate (0.1 ml). The reaction mixture was stirred at ambient temperature for 14 hours. The mixture was evaporated in vacuo, and the resulting residue was triturated with isopropyl ether to give
5 6-(3-isopropylureidomethyl)-2,3-bis(4-methoxyphenyl)-
10 pyridine (0.24 g).

mp : 120°C (dec.)
IR (Nujol) : 3300, 1610, 1565, 1500 cm^{-1}
NMR (CDCl_3 , δ) : 1.13 (6H, d, $J=6.5\text{Hz}$), 3.80 (3H, s),
15 3.81 (3H, s), 3.90 (1H, m), 4.52 (2H, d, $J=5\text{Hz}$),
4.71 (1H, br), 5.54 (1H, br), 6.73-6.86 (4H, m),
7.0-7.4 (7H, m), 7.64 (1H, d, $J=8\text{Hz}$)
MASS (m/z) : 405 (M^+)

The following compound was obtained according to a
20 similar manner to that of Example 17-(1).

(2) 4,5-Bis(4-methoxyphenyl)-2-(3-isopropylureidomethyl)-
pyrimidine
NMR (DMSO-d_6 , δ) : 1.05 (6H, d, $J=7\text{Hz}$), 3.69 (1H, m),
25 3.72 (6H, s), 4.45 (2H, d, $J=6\text{Hz}$), 6.15 (1H, d,
 $J=8\text{Hz}$), 6.28 (1H, t, $J=6\text{Hz}$), 6.88 (2H, d,
 $J=9\text{Hz}$), 6.91 (2H, d, $J=9\text{Hz}$), 7.18 (2H, d,
 $J=9\text{Hz}$), 7.40 (2H, d, $J=9\text{Hz}$), 8.64 (1H, s)
MASS (m/z) : 406 (M^+)

30

Example 18

(1) A mixture of 1,2-bis(4-methoxyphenyl)-3-
dimethylamino-2-propen-1-one (3.1 g), dicyandiamide (1.68
g) and 28% sodium methylate-methanol solution (4 ml) in
35 ethanol (50 ml) was refluxed for 5 hours under stirring.

- 71 -

The reaction mixture was evaporated in vacuo and the residue was dissolved in a mixture of ethyl acetate and water. The resultant solution was adjusted to pH 7.0 with 10% hydrochloric acid. The separated organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel and eluted with a mixture of chloroform and methanol (97:3). The eluted solution was evaporated in vacuo and the residue was recrystallized from a mixture of ethyl acetate and diisopropyl ether to give 4,5-bis(4-methoxyphenyl)-2-cyanoaminopyrimidine (2.0 g).

mp : 208°C (dec.)
IR (Nujol) : 2220, 2100, 1610, 1580 cm^{-1}
15 NMR (DMSO-d₆, δ) : 3.80 (6H, s), 6.91 (2H, d, J=9Hz), 6.93 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.40 (2H, d, J=9Hz), 8.48 (1H, s)
MASS (m/z) : 332 (M⁺)

20 The following compounds were obtained according to a similar manner to that of Example 18-(1).

(2) 2-Acetylaminomethyl-4,5-bis(4-methoxyphenyl)-pyrimidine
25 NMR (DMSO-d₆, δ) : 1.95 (3H, s), 3.64 (3H, s), 3.67 (3H, s), 4.50 (2H, d, J=6Hz), 6.83 (2H, d, J=9Hz), 6.90 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz), 8.45 (1H, m), 8.60 (1H, s)

30 (3) 4,5-Bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine
mp : 131-132.5°C
IR (Nujol) : 1650, 1605, 1580, 1560, 1500 cm^{-1}

- 72 -

Example 19

(1) A mixture of 1,2-bis(4-methoxyphenyl)-3-dimethylamino-2-propen-1-one (3.1 g), 4-amidino-morpholine hydrobromide (4.2 g) and 28% sodium methylate-methanol solution (4 ml) in ethanol (30 ml) was refluxed for 7 hours under stirring. The reaction mixture was evaporated in vacuo and the residue was dissolved in a mixture of ethyl acetate and 10% hydrochloric acid. The separated-aqueous layer was adjusted to pH 8.0 with 20% aqueous potassium carbonate and evaporated with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo and the residue was recrystallized from a mixture of ethyl acetate and diisopropyl ether to give 4,5-bis(4-methoxyphenyl)-2-morpholino pyrimidine (0.47 g).

mp : 147-150°C.

IR (Nujol) : 1605, 1585, 1570, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 3.73 (6H, s), 3.73 (8H, s),

6.80 (2H, d, J=8Hz), 6.85 (2H, d, J=9Hz),

7.05 (2H, d, J=9Hz), 7.32 (2H, d, J=9Hz),

8.26 (1H, s)

Elemental Analysis Calcd. for C₂₂H₂₃N₃O₃ :

C 70.01, H 6.14, N 11.13

Found : C 70.25, H 6.26, N 11.25

25

The following compounds were obtained according to a similar manner to that of Example 19-(1).

30 (2) 4,5-Bis(4-methoxyphenyl)-2-(pyridin-4-yl)pyrimidine

mp : 175-177°C

IR (Nujol) : 1600, 1590, 1565, 1550, 1500 cm⁻¹

NMR (DMSO-d₆, δ) : 3.80 (6H, s), 6.90 (2H, d, J=9Hz),

6.95 (2H, d, J=9Hz), 7.25 (2H, d, J=9Hz),

- 73 -

7.50 (2H, d, J=9Hz), 8.30 (2H, dd, J=2, 5Hz),
8.78 (2H, dd, J=2, 5Hz), 8.83 (1H, s)

MASS (m/z) : 370 ($M^+ + 1$)

5 (3) 4,5-Bis(4-methoxyphenyl)-2-(2,6-dimethylmorpholino)-pyrimidine

mp : 138-140°C

IR (Nujol) : 1610, 1590, 1570, 1500 cm^{-1}

NMR (DMSO-d₆, δ) : 1.17 (6H, d, J=6Hz),
10 2.30-2.70 (2H, m), 3.35-3.80 (2H, m), 3.73 (6H, s),
4.40-4.72 (2H, m), 8.78 (2H, d, J=9Hz),
6.82 (2H, d, J=9Hz), 7.03 (2H, d, J=9Hz),
7.32 (2H, d, J=9Hz), 8.32 (1H, s)

MASS (m/z) : 405 (M^+)

15 Elemental Analysis Calcd. for C₂₄H₂₇N₃O₃ :
C 71.09, H 6.71, N 10.36
Found : C 70.82, H 6.69, N 10.30

Example 20

20 A solution of 4,5-bis(4-methoxyphenyl)-2-(pyridin-4-yl)pyrimidine (2.6 g) and 3-fluorobenzyl iodide (2.36 g) in a mixture of chloroform and methanol (2:4)(30 ml) was allowed to stand at ambient temperature for 2 days. The reaction mixture was evaporated in vacuo and the residue containing 4-[4,5-bis(4-methoxyphenyl)pyrimidin-2-yl]-1-(3-fluorobenzyl)pyridinium iodide was dissolved in a mixture of methanol (40 ml), chloroform (10 ml) and water (10 ml). To the resulting solution was added portionwise sodium borohydride (0.54 g) with stirring at 5 to 10°C.
25 The reaction mixture was stirred for one hour at the same temperature. The reaction mixture was evaporated in vacuo. The residue was dissolved in chloroform and washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo and the residue was subjected to column chromatography on silica
30
35

gel and eluted with a mixture of chloroform and acetone (19:1). The eluted solution was concentrated in vacuo and the crystalline residue was collected by filtration and dried in vacuo to give 4,5-bis(4-methoxyphenyl)-2-[1-(3-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidine (1.33 g).

mp : 130-132°C
IR (Nujol) : 1660, 1615, 1560, 1505 cm⁻¹
NMR (DMSO-d₆, δ) : 2.55-2.77 (4H, m), 3.03-3.27 (2H, m), 3.60 (2H, s), 3.71 (3H, s), 3.77 (3H, s), 6.77 (2H, d, J=9Hz), 6.85 (2H, d, J=9Hz), 7.10 (2H, d, J=9Hz), 7.31 (2H, d, J=9Hz), 6.70-7.40 (5H, m), 8.53 (1H, s)

15 Example 21

(1) A solution of 4,5-bis(4-methoxyphenyl)-2-(pyridin-4-yl)pyrimidine (3.7 g) and methyl iodide (4 ml) in a mixture of chloroform and methanol (9:1) (30 ml) was allowed to stand at ambient temperature for 2 days. The reaction mixture was evaporated in vacuo and the residue was dissolved in a mixture of methanol (50 ml) and water (10 ml). To the resultant solution was added portionwise sodium borohydride (0.76 g) under stirring at 5 to 10°C. The reaction mixture was stirred for one hour at the same temperature. Water (16 ml) was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was dissolved in chloroform and washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo, and the residue was recrystallized from an aqueous methanol to give 4,5-bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine (1.7 g).

mp : 131-132.5°C
IR (Nujol) : 1650, 1605, 1580, 1560, 1500 cm⁻¹
NMR (DMSO-d₆, δ) : 2.30 (3H, s), 2.40-2.80 (4H, m),

3.00-3.20 (2H, m), 3.75 (3H, s), 3.77 (3H, s),
6.83 (2H, d, J=9Hz), 6.89 (2H, d, J=9Hz),
7.13 (2H, d, J=7Hz), 7.18 (1H, s), 7.37 (2H,
d, J=9Hz), 8.58 (1H, s)

5

(2) 4,5-Bis(4-methoxyphenyl)-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine was obtained according to a similar manner to that of Example 21-(1). The product obtained above was dissolved in a solution of hydrochloric acid-ethanol and the resultant solution was evaporated in vacuo. The residue was recrystallized from a mixture of ethanol and ether to give 4,5-bis(4-methoxyphenyl)-2-(1-ethyl-1,2,3,6-tetrahydro pyridin-4-yl)pyrimidine hydrochloride.

15

mp : 183-186°C (dec.)

IR (Nujol) : 1660, 1610, 1590, 1565, 1510 cm^{-1}

NMR (DMSO-d₆, δ) : 1.35 (3H, t, J=7Hz),

3.05-4.13 (6H, m), 3.04 (2H, m),

3.52-4.18 (2H, m), 6.90 (2H, d, J=9Hz),

20

6.96 (2H, d, J=9Hz), 7.18 (1H, s),

7.20 (2H, d, J=9Hz), 7.42 (2H, d, J=9Hz),

8.72 (1H, s)

25

The following compounds were obtained according to a

similar manner to that of Example 21-(1).

(3) 2,3-Bis(4-methoxyphenyl)-6-[1-(4-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]pyridine

mp : 115-117°C

30

IR (Nujol) : 1600, 1580, 1545, 1500 cm^{-1}

NMR (DMSO-d₆, δ) : 2.64 (4H, br s), 3.12 (2H, br s),

3.59 (2H, s), 3.73 (3H, s), 3.74 (3H, s),

6.72-7.07 (5H, m), 7.11-7.42 (8H, m),

7.47 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz)

35

MASS (m/z) : 481 (M⁺)

- 76 -

- (4) 4,5-Bis(4-methoxyphenyl)-2-[1-(4-fluorobenzyl)-
1,2,3,6-tetrahydropyridin-4-yl]pyrimidine

mp : 118-120°C

IR (Nujol) : 1645, 1600, 1570, 1500 cm⁻¹

NMR (DMSO-d₆, δ) : 2.67 (4H, br s), 3.17 (2H, br s),
3.61 (2H, s), 3.75 (3H, s), 3.77 (3H, s), 6.87
(2H, d, J=9Hz), 6.94 (2H, d, J=9Hz), 7.11-7.20
(3H, m), 7.13 (2H, d, J=9Hz), 7.33 (2H, d,
J=9Hz), 7.20-7.42 (2H, m), 8.64 (1H, s)

10

- (5) 4,5-Bis(4-methoxyphenyl)-2-[1-(2-phenylethyl)-
1,2,3,6-tetrahydropyridin-4-yl]pyrimidine

mp : 135-136°C

IR (Nujol) : 1600, 1560, 1500 cm⁻¹

NMR (DMSO-d₆, δ) : 2.70-2.85 (8H, m), 3.27-3.35 (2H,
m), 3.76 (6H, s), 6.87 (2H, d, J=9Hz), 6.94 (2H,
d, J=9Hz), 7.16-7.33 (6H, m), 7.46 (2H, d,
J=9Hz), 8.65 (1H, s)

MASS (m/z) : 477 (M⁺)

20

- (6) 4,5-Bis(4-methoxyphenyl)-2-[1-(2-fluorobenzyl)-
1,2,3,6-tetrahydropyridin-4-yl]pyrimidine

mp : 96-99°C

IR (Nujol) : 1650, 1600, 1570, 1550 cm⁻¹

NMR (DMSO-d₆, δ) : 2.69 (4H, br s), 3.23 (2H, br s),
3.68 (2H, s), 3.75 (3H, s), 3.77 (3H, s), 6.86
(2H, d, J=9Hz), 6.93 (2H, d, J=9Hz), 7.18 (2H,
d, J=9Hz), 7.13-7.47 (5H, m), 7.39 (2H, d,
J=9Hz), 8.67 (1H, s)

MASS (m/z) : 481 (M⁺)

- (7) 4,5-Bis(4-methoxyphenyl)-2-[1-benzyl-1,2,3,6-
tetrahydropyridin-4-yl]pyrimidine

mp : 128-130°C

IR (Nujol) : 1645, 1600, 1570, 1545 cm⁻¹

35

- 77 -

NMR (DMSO-d₆, δ) : 2.50 (4H, br s), 3.20 (2H, br s),
3.63 (2H, s), 3.75 (3H, s), 3.77 (3H, s), 6.87
(2H, d, J=9Hz), 6.93 (2H, d, J=9Hz), 7.17 (2H,
d, J=9Hz), 7.16-7.42 (5H, m), 7.25 (1H, s), 7.39
(2H, d, J=9Hz), 8.64 (1H, s)

5

MASS (m/z) : 463 (M⁺)

Example 22

(1) A mixture of 4,5-bis(4-methoxyphenyl)-(1-methyl-
10 1,2,3,6-tetrahydropyridin-4-yl)pyrimidine (2.10 g), 10%
palladium-carbon (0.6 g) and ammonium formate (1.71 g) in
acetic acid (40 ml) was stirred at 100 to 110°C for 2
hours. The reaction mixture was filtered and the filtrate
was evaporated in vacuo. The residue was dissolved in a
15 mixture of ethyl acetate, tetrahydrofuran and water and
the resulting mixture was adjusted to pH 8.0 with 20%
aqueous potassium carbonate. The separated organic layer
was washed with brine and dried over magnesium sulfate.
After filtration, the filtrate was evaporated in vacuo and
20 the residue was subjected to column chromatography on
silica gel and eluted with a mixture of chloroform and
methanol (8:2). The eluted solution was evaporated in
vacuo and the oily residue was dissolved in a solution of
hydrochloric acid-ethanol and the resultant solution was
25 evaporated in vacuo and the residue was recrystallized
from a mixture of ethanol and ether to give 4,5-bis(4-
methoxyphenyl)-2-(1-methylpiperidin-4-yl)pyrimidine
dihydrochloride (0.34 g).

mp : 227-230°C (dec.)

30 IR (Nujol) : 1590, 1510 cm⁻¹

NMR (DMSO-d₆, δ) : 2.02-2.20 (4H, m), 2.72 (3H, s),
2.96-3.64 (6H, m), 3.77 (5H, s), 6.90 (2H, d,
J=9Hz), 6.96 (2H, d, J=9Hz), 7.21 (2H, d,
J=9Hz), 7.42 (2H, d, J=9Hz), 8.72 (1H, s)

The following compound was obtained according to a similar manner to that of Example 22-(I).

5 4,5-Bis(4-methoxyphenyl)-2-[1-(3-fluorobenzyl)-piperidin-4-yl]pyrimidine hydrochloride
mp : 207-211°C (dec.)
IR (Nujol) : 1595, 1510 cm⁻¹
10 NMR (DMSO-d₆, δ) : 2.16-2.22 (4H, m), 3.00-3.54 (5H, m), 3.77 (2H, s), 4.39 (2H, d, J=5Hz), 6.85 (2H, d, J=9Hz), 6.96 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.41 (2H, d, J=9Hz), 7.27-7.75 (4H, m), 8.70 (1H, s)

Example 23

15 (1) A solution of 4,5-bis(4-methoxyphenyl)-2-cyanoaminopyrimidine (1.0 g) and morpholine (1.3 g) in ethanol (10 ml) was refluxed for one hour under stirring. The reaction mixture was evaporated in vacuo and the residue was dissolved in a mixture of ethyl acetate and 10% hydrochloric acid. The separated aqueous layer was adjusted to pH 8.0 with 20% aqueous potassium carbonate and extracted with a mixture of ethyl acetate and tetrahydrofuran. The organic layer was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo and the residue was recrystallized from a mixture of ethyl acetate and ether to give 4,5-bis(4-methoxyphenyl)-2-[(4-morpholinocarboximidoyl)amino]pyrimidine (0.72 g).

20 mp : 176-178°C
IR (Nujol) : 3270, 3150, 1610, 1590 cm⁻¹
25 NMR (DMSO-d₆, δ) : 3.33 (4H, s), 3.60 (4H, s), 3.75 (6H, s), 6.83 (2H, d, J=9Hz), 6.85 (2H, d, J=9Hz), 7.08 (2H, d, J=7Hz), 7.28 (2H, d, J=9Hz), 8.36 (1H, s), 8.37 (2H, s)
30 MASS (m/z) : 419 (M⁺)

- 79 -

Elemental Analysis Calcd. for $C_{23}H_{25}N_5O_3$:
C 65.85, H 6.01, N 16.70
Found : C 65.60, H 6.07, N 16.67

The following compounds were obtained according to a similar manner to that of example 23-(1).

- (2) 4,5-Bis(4-methoxyphenyl)-2-[(4-methyl-1-piperazinecarboximidoyl)amino]pyrimidine
mp : 138-140°C (dec.)
IR (Nujol) : 3280, 3130, 1610, 1590, 1510 cm^{-1}
NMR (DMSO-d₆, δ) : 2.19 (3H, s), 2.00-2.43 (4H, m),
3.40-3.70 (4H, m), 3.73 (6H, s), 6.84 (2H, d,
J=9Hz), 6.86 (2H, d, J=9Hz), 7.06 (2H, d,
J=9Hz), 7.27 (2H, d, J=9Hz), 8.33 (1H, s),
8.10-8.66 (2H, m)
MASS (m/z) : 432 (M⁺)
- (3) 4,5-Bis(4-methoxyphenyl)-2-[(4-benzyl-1-piperazinecarboximidoyl)amino]pyrimidine
mp : 175-177°C
IR (Nujol) : 3300, 3150, 1605, 1580, 1505 cm^{-1}
NMR (DMSO-d₆, δ) : 2.40 (4H, br s), 3.31-3.60 (6H,
m), 3.74 (6H, s), 6.78-7.05 (4H, m),
7.13 (2H, d, J=9Hz), 7.23-7.38 (8H, m),
8.35 (1H, s), 8.35-8.43 (2H, m)
MASS (m/z) : 508 (M⁺)
- (4) 4,5-Bis(4-methoxyphenyl)-2-[3-(1-benzylpiperidin-4-yl)guanidino]pyrimidine
mp : 157-159°C (dec.)
IR (Nujol) : 3150, 3300, 1640 (sch), 1605, 1580 cm^{-1}
NMR (DMSO-d₆, δ) : 1.17-1.52 (2H, m), 1.81-2.28 (4H,
m), 2.67-2.73 (2H, m), 3.44 (2H, s), 3.75 (6H,
s), 3.64-3.89 (1H, m), 6.82 (2H, d, J=9Hz),

- 80 -

6.91 (2H, d, J=9Hz), 7.11 (2H, d, J=9Hz),
7.19-7.40 (8H, m), 8.48 (1H, s)

MASS (m/z) : 522 (M^+)

- 5 (5) 4,5-Bis(4-methoxyphenyl)-2-[(4-benzyl-1-piperidine-
carboximidoyl)amino]pyrimidine
mp : 160°C (dec.)
IR (Nujol) : 3300, 3150, 1600, 1580, 1520 cm^{-1}
NMR (DMSO-d₆, δ) : 1.02-1.15 (2H, m), 1.57-1.78 (3H,
10 m), 2.70-2.82 (2H, m), 3.22-3.86 (2H, m), 3.75
 m), 4.33-4.40 (2H, m), 6.83-6.90 (4H, m),
 7.07 (2H, d, J=9Hz), 7.10-7.31 (8H, m), 8.33
 (1H, s), 8.37 (2H, br s)
MASS (m/z) : 507 (M^+)
- 15 (6) 4,5-Bis(4-methoxyphenyl)-2-[{4-(2-methoxyphenyl)-1-
piperazinecarboximidoyl}amino]pyrimidine
mp : 199-200°C
IR (Nujol) : 3320, 3180, 1605, 1570, 1515 cm^{-1}
20 NMR (DMSO-d₆, δ) : 3.00 (4H, br s), 3.75 (9H, s),
 3.82 (4H, br s), 6.84-7.07 (8H, m), 7.15 (2H, d,
 J=9Hz), 7.31 (2H, d, J=9Hz), 8.38 (1H, s), 8.49
 (2H, br s)
- 25 Example 24
(1) A solution of 4,5-bis(4-methoxyphenyl)-2-cyanoamino
pyrimidine (1.0 g) and piperidine (1.1 g) in methyl
cellosolve (5 ml) was stirred at 120 to 125°C for 3 hours.
The reaction mixture was poured into water and extracted
with ethyl acetate. The extract was washed with brine and
dried over magnesium sulfate. After filtration, the
filtrate was evaporated in vacuo and the residue was
recrystallized from a mixture of ethyl acetate and
diisopropyl ether to give 4,5-bis(4-methoxyphenyl)-
30 2-[(1-piperidinecarboximidoyl)amino]pyrimidine (0.65 g).
35

- 81 -

mp : 185-187°C

IR (Nujol) : 3330, 3170, 1610, 1590, 1565, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 1.30-1.70 (6H, m), 3.40-3.70 (4H, m), 3.73 (6H, s), 6.81 (2H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 7.05 (2H, d, J=9Hz), 7.27 (2H, d, J=9Hz), 8.30 (1H, s), 8.32 (2H, m)

5

The following compounds were obtained according to a similar manner to that of Example 24-(1).

10

(2) 4,5-Bis(4-methoxyphenyl)-2-(3-cyclohexylguanidino)-pyrimidine

mp : 203-205°C

IR (Nujol) : 3310, 3205, 1595, 1510 cm⁻¹

15

NMR (DMSO-d₆, δ) : 0.86-2.03 (11H, m), 3.75 (6H, s), 6.85 (2H, d, J=9Hz), 6.88 (2H, d, J=9Hz), 7.10 (2H, d, J=9Hz), 7.30 (2H, d, J=9Hz), 8.47 (1H, s)

MASS (m/z) : 431 (M⁺)

20

(3) 4,5-Bis(4-methoxyphenyl)-2-[(2-imidazolin-2-yl)-amino]pyrimidine

mp : 190-192°C

IR (Nujol) : 3460, 3320, 3200, 1640, 1610, 1585, 1575, 15105 cm⁻¹

25

NMR (DMSO-d₆, δ) : 3.10-3.45 (4H, m), 3.73 (6H, s), 6.60 (2H, s), 6.80 (2H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 7.03 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 8.15 (1H, s)

30

(4) 4,5-Bis(4-methoxyphenyl)-2-(3-isopropylguanidino)-pyrimidine

mp : 167-169°C (dec.)

IR (Nujol) : 3350, 3170, 1680, 1640, 1610, 1580, 1530 cm⁻¹

35

- 82 -

NMR (DMSO-d₆, δ) : 1.18 (6H, d, J=5Hz), 3.40-4.00
(1H, m), 3.75 (6H, s), 6.60-7.50 (8H, m), 8.46
(1H, s)
MASS (m/z) : 391 (M⁺)

5

(5) 4,5-Bis(4-methoxyphenyl)-2-(3-benzylguanidino)-
pyrimidine

mp : 204-206°C

IR (Nujol) : 3460, 1630, 1610, 1560 cm⁻¹

10

NMR (DMSO-d₆, δ) : 3.80 (6H, s), 4.62 (2H, s),
6.92 (2H, d, J=9Hz), 6.97 (2H, d, J=9Hz),
7.20 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz),
7.43 (5H, s), 8.43 (1H, s)

15

Example 25

A solution of 4,5-bis(4-methoxyphenyl)-2-cyanoamino pyrimidine (0.67 g) and dimethylamine hydrochloride (0.4 g) in ethanol (20 ml) was refluxed for 10 hours under stirring. The reaction mixture was evaporated in vacuo and the residue was dissolved in a mixture of ethyl acetate and 10% hydrochloric acid. The separated aqueous layer was adjusted to pH 8.0 with 20% aqueous potassium carbonate and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was evaporated in vacuo and the oily residue was dissolved in a hydrochloric acid ethanol solution. The resultant mixture was evaporated in vacuo and the residue was recrystallized from a mixture of ethanol and ether to give 4,5-bis(4-methoxyphenyl)-2-(3,3-dimethylguanidino)pyrimidine hydrochloride (0.28 g).

30

mp : 238-239°C

IR (Nujol) : 3130, 1640, 1605, 1580 cm⁻¹

35

NMR (DMSO-d₆, δ) : 3.20 (6H, s), 3.78 (6H, s),
6.88 (2H, d, J=7Hz), 6.95 (2H, d, J=9Hz),
7.17 (2H, d, J=9Hz), 7.39 (2H, d, J=9Hz),

- 83 -

8.62 (1H, s), 9.22 (2H, m)

MASS (m/z) : 377 (M^+)

Elemental Analysis Calcd. for $C_{21}H_{23}N_5O_2$:

C 60.94, H 5.84, N 16.92, Cl 8.57

5 Found : C 60.90, H 5.64, N 16.78, Cl 8.64

Example 26

A mixture of 2,3-bis(4-methoxyphenyl)pyrazine-5-carboxylic acid (1.01 g), 1-hydroxybenzotriazole (446 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (573 mg) in N,N-dimethylformamide (20 ml) was stirred for 1 hour at ambient temperature. N-methyl piperazine (500 mg) was added thereto, and the mixture was stirred for 2 hours. After the solvent was removed, to the residue were added chloroform (30 ml) and water (20 ml), and the mixture was adjusted to pH 9 with a saturated aqueous solution of potassium carbonate. The separated organic layer was washed with water (20 ml), dried over magnesium sulfate and concentrated. The residue was dissolved with ethyl acetate (20 ml) and crystallized with a diethyl ether solution saturated with hydrogen chloride and the precipitate was collected and washed with ethyl acetate to give 2,3-bis(4-methoxyphenyl)-5-[(4-methylpiperazin-1-yl)carbonyl]pyrazine hydrochloride.

25 mp : 90-93°C

IR (Nujol) : 1630, 1600, 1505 cm^{-1}

NMR (D_2O , δ) : 3.23 (3H, s), 3.70 (6H, s),
3.1-4.3 (8H, m), 6.6-7.1 (4H, m), 7.2-7.7 (4H,
m), 9.03 (1H, s)

30 MASS (m/z) : 418 (M^+ of free compound)

Example 27

(1) A mixture of 2,3-bis(4-methoxyphenyl)pyrazine-5-carboxylic acid (1.03 g), 1-hydroxybenzotriazole (446 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (573 mg) in N,N-dimethylformamide (20 ml) was stirred for 1 hour at ambient temperature. 30% Methylamine-methanol solution (5 ml) was added thereto, and the mixture was stirred for 3 hours. After the solvent was removed, to the residue were added chloroform (30 ml) and water (20 ml), and the mixture was adjusted to pH 9 with a saturated aqueous solution of potassium carbonate. The separated organic layer was dried over magnesium sulfate and concentrated. The residue was subjected to column chromatography on silica gel (50 g) and eluted with 15% solution of methanol in chloroform. The fractions containing the desired compound were collected and concentrated. The residue was crystallized with a diethyl ether solution saturated with hydrogen-chloride to give 2,3-bis(4-methoxyphenyl)-5-(methylcarbamoyl)pyrazine hydrochloride.

mp : 125-127°C
IR (Nujol) : 1680, 1600, 1520, 1510 cm^{-1}
NMR (DMSO-d_6 , δ) : 2.87 (3H, d, $J=5\text{Hz}$), 3.77 (6H, s), 6.93 (4H, d, $J=10\text{Hz}$), 7.3-7.6 (4H, m), 8.72 (1H, d, $J=5\text{Hz}$), 9.03 (1H, s)
MASS (m/z) : 349 (M^+ of free compound)

The following compound was obtained according to a similar manner to that of Example 27-(1).

(2) 2,3-Bis(4-methoxyphenyl)-5-[(1-benzylpiperidin-4-yl)-carbamoyl]pyrazine
mp : 157-159°C
IR (Nujol) : 3400, 1655, 1600, 1500 cm^{-1}
NMR (CDCl_3 , δ) : 1.5-2.33 (6H, m), 2.77-3.0 (2H, m), 3.53 (2H, s), 3.82 (3H, s), 3.85 (3H, s), 3.95-4.2 (1H, m), 6.8-7.02 (4H, m), 7.15-7.53 (10H, m), 7.76 (1H, d, $J=8.5\text{Hz}$), 9.28 (1H, s)
MASS (m/z) : 508 (M^+)

Example 28

A mixture of 5-chloro-2,3-(4-methoxyphenyl)pyrazine (653 mg) and guanidine carbonate (900 mg) in N,N-dimethyl formamide (5 ml) was heated at 140°C for 15 hours. After 5 the solvent was removed under reduced pressure, to the residue were added water (15 ml) and 5% methanol in chloroform (30 ml). The separated organic layer was washed with saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was removed 10 and the residue was subjected to column chromatography on silica gel (50 g) and eluted with 10% solution of methanol in chloroform, the fractions containing the desired compound were collected and concentrated. The residue was pulverized with diethyl ether to give 15 5-(N,N-dimethylamino)-2,3-bis(4-methoxyphenyl)pyrazine.

mp : 161-163°C
IR (Nujol) : 1605, 1555, 1490 cm^{-1}
NMR (DMSO-d₆, δ) : 3.10 (6H, s), 3.68 (6H, s),
6.80 (2H, d, J=10Hz), 6.82 (2H, d, J=10Hz),
20 7.20 (2H, d, J=10Hz), 7.30 (2H, d, J=10Hz),
8.07 (1H, s)
MASS (m/z) : 335 (M⁺)

Example 29

25 A mixture of 5-chloro-2,3-bis(4-methoxyphenyl)-pyrazine (980 mg) and guanidine (1.8 g) and N,N-dimethylformamide (1.0 ml) was heated at 150°C for 8 hours. After the solvent was removed under reduced pressure, the residue was subjected to column 30 chromatography on silica gel (50 g) and eluted with 15% solution of methanol in chloroform. The fractions containing the desired compound were collected and concentrated. The residue was dissolved in ethyl acetate (20 ml) and crystallized with an ethanol solution saturated 35 with hydrogen chloride. The precipitate was collected and

- 86 -

washed with ethyl acetate to give 5-guanidino-2,3-bis(4-methoxyphenyl)pyrazine hydrochloride.

mp : 246-269°C (dec.)

IR (Nujol) : 3250, 1680, 1620, 1600, 1510 cm^{-1}

5 NMR (DMSO-d₆, δ) : 3.74 (6H, s), 6.7-7.0 (4H, m),
7.2-7.5 (4H, m), 8.38 (5H, s)

MASS (m/z) : 349 (M⁺)

Example 30

10 A mixture of morpholine (3 ml) and
5-chloro-2,3-bis(4-methoxyphenyl)pyrazine (980 mg) was
stirred at 100°C for 3 hours. The solvent was removed
under reduced pressure and the residue was crystallized
with ether to give 2,3-bis(4-methoxyphenyl)-5-(morpholin-4-yl)-pyrazine.

15 mp : 138-139°C

IR (Nujol) : 1603, 1573, 1545, 1505 cm^{-1}

NMR (CDCl₃, δ) : 3.5-4.0 (8H, m), 3.76 (6H, s),
6.89 (4H, d, J=10Hz), 7.2-7.5 (4H, m),

8.03 (1H, s)

20 MASS (m/z) : 377 (M⁺)

Example 31

A mixture of piperazine (5 g) and 5-chloro-
2,3-bis(4-methoxyphenyl)pyrazine (980 mg) in ethanol (10
ml) was refluxed for 3 hours. After the solvent was
removed, to the residue were added ethyl acetate (20 ml)
and water (30 ml). The separated organic layer was washed
with a saturated aqueous solution of sodium chloride and
dried over magnesium sulfate. After the solvent was
removed, the residue was crystallized with ether to give
2,3-bis(4-methoxyphenyl)-5-(piperazin-1-yl)pyrazine.

30 mp : 128-129°C

IR (Nujol) : 3400, 1605, 1570, 1545, 1510 cm^{-1}

35 NMR (DMSO-d₆, δ) : 2.6-2.9 (4H, m), 3.4-3.6 (4H, m),

3.73 (6H, s), 6.82 (4H, d, J=9Hz),
7.12-7.43 (4H, m), 8.12 (1H, s)

MASS (m/z) : 376 (M^+)

5 Example 32

A mixture of 5-chloro-2,3-bis(4-methoxyphenyl)pyrazine (980 mg) and N-methylpiperazine (3 ml) was stirred at 60°C for 3 hours and at 100°C for 2 hours. After the solvent was removed under reduced pressure, the residue was dissolved in diethyl ether (30 ml) and crystallized with an ether solution saturated with hydrogen chloride. The precipitate was collected and washed with ether to give 2,3-bis(4-methoxyphenyl)-5-(4-methylpiperazin-1-yl)-pirazine dihydrochloride.

15 mp : 187-189°C

IR (Nujol) : 1600, 1570, 1510, 1490 cm^{-1}

NMR (DMSO-d₆, δ) : 2.79 (3H, d, J=5Hz), 2.9-4.7 (8H, m), 3.74 (6H, s), 6.8-7.4 (10H, m), 8.36 (1H, s)

MASS (m/z) : 390 (M^+ of free compound)

20

Example 33

A mixture of 2,3-bis(4-methoxyphenyl)-5-methyl pyrazine (1.07 g), dimethylamine hydrochloride (346 mg) and paraformaldehyde (126 mg) in acetic acid (3 ml) was stirred for 10 days at ambient temperature. After the solvent was removed, to the residue were added water (10 ml) and 5% solution of methanol in chloroform (20 ml), and the mixture was adjusted to pH 9 with a saturated aqueous solution of potassium carbonate. The separated organic layer was dried over magnesium sulfate. The solvent was removed and the residue was subjected to column chromatography on silica gel (50 g) and eluted with 10% solution of methanol in chloroform. The fractions containing the desired compound were collected and concentrated. The residue was dissolved in ethyl acetate

(30 ml) and crystallized with a solution of hydrogen chloride in ether to give 5-[2-(N,N-dimethylamino)ethyl]-2,3-bis(4-methoxyphenyl)pyrazine hydrochloride.

mp : 203-207°C (dec.)

IR (Nujol) : 3350, 2600, 1600, 1520 cm^{-1}
5 NMR (D_2O , δ) : 2.8-3.2 (2H, m), 3.0 (6H, s),
3.6-4.0 (2H, m), 3.85 (6H, s), 6.8-7.6 (8H, m),
8.83 (1H, s)
MASS (m/z) : 363 (M^+)

10

Example 34

A mixture of 3-(2-t-butoxycarbonylaminoethyl)-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (5.00 g) and 2.5-norbornadiene (12.0 ml) in xylene (200 ml) was refluxed under stirring for 3 days. The reaction mixture was evaporated in vacuo. To the residue was added 4N-1,4-dioxane solution of hydrogen chloride and the mixture was stirred at 0°C for 2 hours. The reaction mixture was evaporated in vacuo. The resulting precipitate was washed with diethyl ether and dried to give 6-(2-aminoethyl)-2,3-bis(4-methoxyphenyl)pyridine hydrochloride (5.35 g).

IR (Nujol) : 1610, 1510, 1300, 1250 cm^{-1}
25 NMR (DMSO-d_6 , δ) : 3.33-3.43 (4H, m), 3.75 (3H, s),
3.78 (3H, s), 6.91 (2H, d, $J=7\text{Hz}$), 6.94 (2H, d,
 $J=7\text{Hz}$), 7.11 (2H, d, $J=7\text{Hz}$), 7.34 (2H, d,
 $J=7\text{Hz}$), 7.76 (1H, d, $J=8\text{Hz}$), 8.19 (1H, d,
 $J=8\text{Hz}$), 8.44 (3H, br s)
MASS (m/z) : 334 (M^+ of free compound)

30

Example 35

(1) A mixture of 3-{N,N-dimethylaminomethyl}-5,6-bis(4-methoxyphenyl)-1,2,4-triazine (0.60 g) and an ethanol solution of hydrogen chloride (15 ml) was stirred at the ambient temperature for 3 hours. The reaction mixture was

- 89 -

evaporated in vacuo and the residue was washed with diethyl ether to give 3-{N,N-dimethylaminomethyl}-5,6-bis(4-methoxyphenyl)-1,2,4-triazine hydrochloride (0.58 g).

5 mp : 215-218°C
IR (Nujol) : 1600, 1300, 1250 cm⁻¹
NMR (DMSO-d₆, δ) : 2.97 (3H, s), 2.99 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 4.85 (2H, d, J=6Hz), 6.98 (2H, d, J=8Hz), 7.03 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz), 7.63 (2H, d, J=8Hz)
10 Mass (m/z) : 350 (M⁺ of free compound)

The following compound was obtained according to a similar manner to that of Example 35-(1)

15 (2) 2,3-Bis(4-methoxyphenyl)-6-(N,N-dimethylaminomethyl)-pyridine dihydrochloride
mp : 80°C-82°C (dec.)
IR (Nujol) : 1600, 1510, 1300, 1250 cm⁻¹
20 NMR (DMSO-d₆, δ) : 2.86 (6H, s), 3.75 (3H, s), 3.76 (3H, s), 4.54 (2H, s), 6.85 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 7.13 (2H, d, J=8Hz), 7.34 (2H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz)

25

30

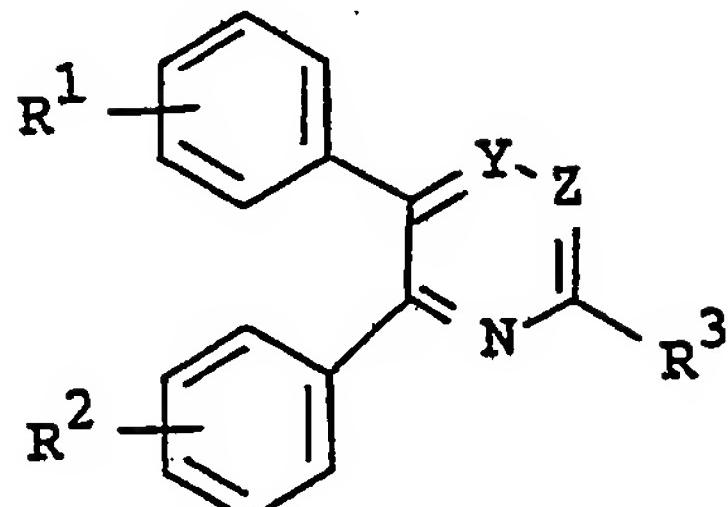
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-90-

C L A I M S

1. A compound of the formula :

5



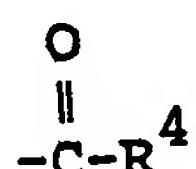
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wherein R¹ and R² are each lower alkoxy,
 R³ is heterocyclic group selected from the
 group consisting of pyridyl,
 tetrahydropyridyl, piperidyl,
 piperazinyl and morpholinyl, which may
 have suitable substituent(s);
 substituted amino;
 carboxy(lower)alkenyl;
 carboxy(lower)alkyl;
 hydroxy(lower)alkyl;
 amino(lower)alkyl which may have
 suitable substituent(s);
 a group of the formula :

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20

25



30

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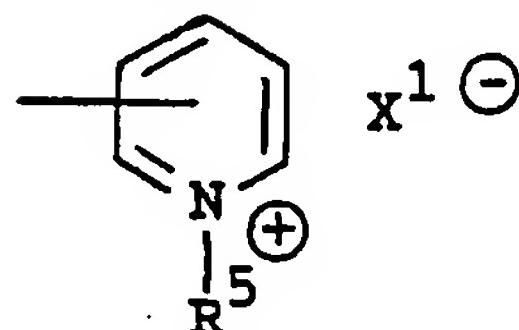
(in which R⁴ is hydrogen, ethoxy,
 mono(or di)lower
 alkylamino, di(lower)-
 alkylamino-(lower)-
 alkylamino,
 heterocyclicamino
 which may have suitable
 substituent(s), or

- 91 -

heterocyclic group which
may have suitable
substituent(s));

or a group of the formula :

5



10

(in which R^5 is lower alkyl or
ar(lower)alkyl
which may have suitable
substituent(s), and
 X^1 is an acid residue),

15

Y is CH or N and
 Z is CH or N,

with proviso that

20

when R^3 is pyridyl; piperidyl which may have hydroxy group; piperazinyl which has lower alkyl group or hydroxy(lower)alkyl group; morpholinyl; lower alkenylamino; hydroxy(lower)alkylamino; phenylamino which may have lower alkoxy group or halogen on the benzene ring; halophenyl(lower)-alkylamino; phenylsulfonylamino which has nitro group, amino group or halogen on the benzene ring; or amino substituted with two substituents selected from the group consisting of lower alkyl and hydroxy(lower)alkyl, and

25

Y is N,

30

then Z is CH,

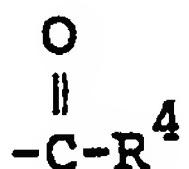
and a pharmaceutically acceptable salt thereof.

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- 92 -

2. A compound of claim 1, wherein
R³ is heterocyclic group selected from the group
consisting of pyridyl, tetrahydropyridyl,
piperidyl, piperazinyl and morpholinyl, which
may have one to three suitable substituent(s);
5 cyanoamino; imidazolinylamino; guanidino;
di(lower)alkylguanidino; lower alkylguanidino;
cyclo(lower)alkylguanidino;
ar(lower)alkylguanidino; heterocyclicguanidino
10 which may be substituted with one to three
suitable substituent(s);
(1-heterocyclic-1-iminomethyl)amino which may
have one to three suitable substituent(s);
di(lower)alkylamino; hydroxy(lower)alkyl;
15 carboxy(lower)alkyl; carboxy(lower)alkenyl;
amino(lower)alkyl which may have one to three
substituent(s) selected from the group
consisting of lower alkyl and acyl;
a group of the formula :

20



25

(in which R⁴ is hydrogen; ethoxy; mono(or
di)lower alkylamino; di(lower)-
alkylamino-(lower)alkylamino;
heterocyclicamino which may have
one to three substituent(s)
selected from the group consisting
of lower alkyl, lower alkoxy,

30

halogen and ar(lower)alkyl; or
heterocyclic group which may have
one to three substituent(s)
selected from the group consisting
of lower alkyl, lower alkoxy,

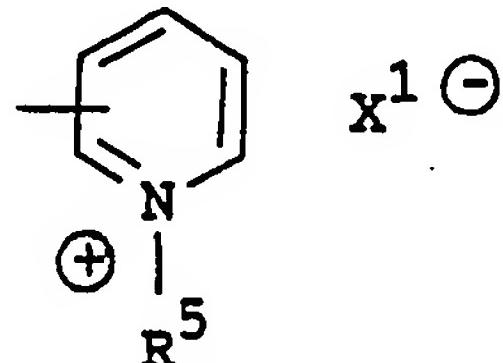
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- 93 -

halogen, ar(lower)alkyl and
hydroxy(lower)alkyl);

or a group of the formula :

5



10

(in which R⁵ is lower alkyl, or ar(lower)alkyl
which may have one to three
substituent(s) selected from the
group consisting of halogen,
lower alkyl and lower alkoxy; and
X¹ is an acid residue).

15

3. A compound of claim 2, wherein
R³ is heterocyclic group selected from the group
consisting of pyridyl, tetrahydropyridyl,
20 piperidyl, piperazinyl and morpholinyl, which
may have one or two substituent(s) selected from
the group consisting of lower alkyl and
ar(lower)alkyl which may have one or two
halogen; cyanoamino; imidazolinylamino;
guanidino; di(lower)alkylguanidino; lower
25 alkylguanidino; cyclo(lower)alkylguanidino;
phenyl(lower)alkylguanidino;
heterocyclicguanidino which may have
ar(lower)alkyl; (1-heterocyclic-1-iminomethyl)-
30 amino which may have substituent selected from
the group consisting of lower alkyl,
ar(lower)alkyl and aryl which may have lower
alkoxy; di(lower)alkylamino;
hydroxy(lower)alkyl; carboxy(lower)alkyl;
35 carboxy(lower)alkenyl; amino(lower)alkyl which

5

may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkanoyl, lower alkylcarbamoyl, lower alkoxy carbonyl and heterocyclic carbonyl which may have one to three suitable substituent(s); a group of the formula :



10

(in which R^4 is hydrogen; ethoxy; mono(or di)lower alkylamino; di(lower)alkylamino-(lower)-alkylamino; saturated 5 or 6-membered heteromonocyclic amino in which heteromonocyclic group contains 1 to 3 nitrogen atom(s), which may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and phenyl(lower)alkyl; saturated 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen, phenyl(lower)alkyl and hydroxy(lower)alkyl; or saturated 5 or 6-membered heteromonocyclic group containing 1 to 3 nitrogen

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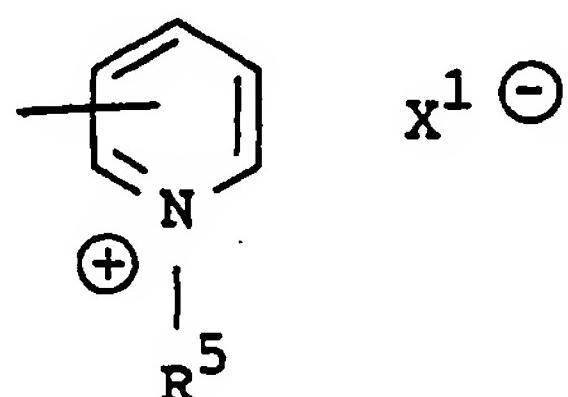
- 95 -

5

atom(s), which may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen, phenyl(lower)alkyl and hydroxy(lower)alkyl);

10

or a group of the formula :



20

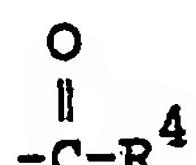
(in which R^5 is lower alkyl, or phenyl(lower)alkyl which may have one or two substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy; and X^1 is halogen).

4. A compound of claim 3, wherein R^3 is heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have one or two substituent(s) selected from the group consisting of lower alkyl, phenyl(lower)alkyl and halophenyl(lower)alkyl; cyanoamino; imidazolinylamino; guanidino; di(lower)alkylguanidino; lower alkylguanidino; cyclo(lower)alkylguanidino; phenyl(lower)alkylguanidino; phenyl(lower)alkylpiperidylguanidino; {morpholinyl(imino)methyl}amino; {piperidyl(imino)methyl}amino which may have

- 96 -

phenyl(lower)alkyl;
 {piperazinyl(imino)methyl}amino which may have
 substituent selected from the group consisting
 of lower alkyl, phenyl(lower)alkyl and lower
 5 alkoxy-phenyl; di(lower)alkylamino;
 hydroxy(lower)alkyl; carboxy(lower)alkyl;
 carboxy(lower)alkenyl; amino(lower)alkyl which
 may have one or two substituent(s) selected from
 the group consisting of lower alkyl, lower
 10 alkanoyl, lower alkylcarbamoyl, lower
 alkoxycarbonyl and tetrahydropyridazinylcarbonyl
 which may have oxo group;
 a group of the formula :

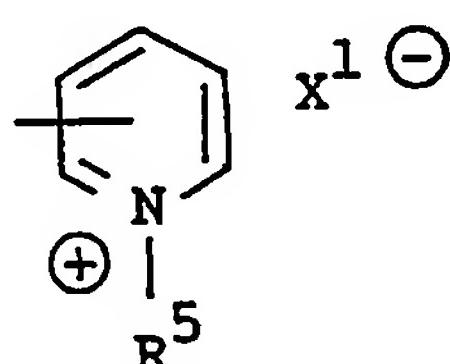
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(in which R^4 is hydrogen, ethoxy, mono(or
 di)lower alkylamino, di(lower)-
 20 alkylamino-(lower)alkylamino,
 phenyl(lower)alkylpiperidylamino,
 morpholinyl, or piperazinyl which
 may have lower alkyl,
 hydroxy(lower)alkyl or
 25 phenyl(lower)alkyl);

or a group of the formula :

30



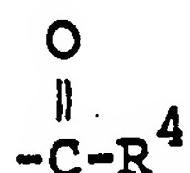
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(in which R^5 is lower alkyl, or
 phenyl(lower)alkyl which may have
 halogen, and
 X^1 is halogen).

- 97 -

5. A compound of claim 4, wherein
 R^3 is a group of the formula :

5



(in which R^4 is lower alkylpiperazinyl),

Y is N and

Z is N.

10

6. A compound of claim 5, which is 5,6-Bis(4-methoxyphenyl)-3-{(4-methylpiperazin-1-yl)carbonyl}-1,2,4-triazine hydrochloride.

15

7. A compound of claim 4, wherein
 R^3 is lower alkyltetrahydropyridyl,
Y is CH and
Z is N.

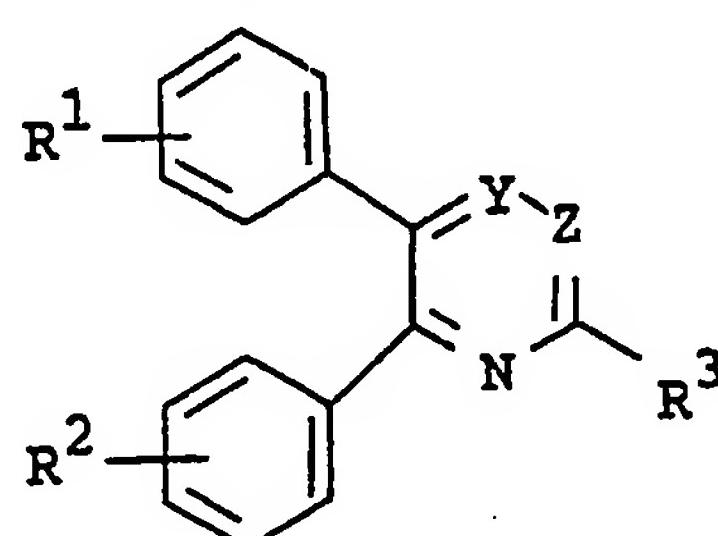
20

8. A compound of claim 7, which is
4,5-Bis(4-methoxyphenyl)-2-(1-methyl-1,2,3,6-tetrahydropyridine-4-yl)pyrimidine.

25

9. A process for preparing a compound of the formula :

30



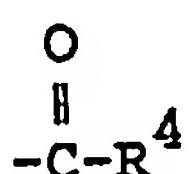
35

wherein R^1 and R^2 are each lower alkoxy,
 R^3 is heterocyclic group selected from the
group consisting of pyridyl,
tetrahydropyridyl, piperidyl,

- 98 -

piperazinyl and morpholinyl, which may have suitable substituent(s);
 substituted amino;
 carboxy(lower)alkenyl;
 5 carboxy(lower)alkyl;
 hydroxy(lower)alkyl;
 amino(lower)alkyl which may have suitable substituent(s);
 a group of the formula :

10



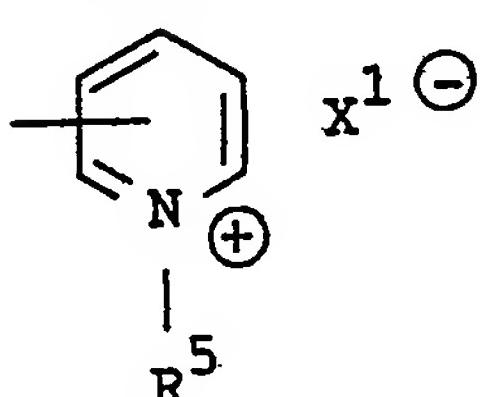
15

(in which R^4 is hydrogen, ethoxy,
 mono(or di)lower-
 alkylamino, di(lower)-
 alkylamino-(lower)-
 alkylamino,
 heterocyclicamino
 which may have suitable
 substituent(s), or
 heterocyclic group which
 may have suitable
 substituent(s));

20

or a group of the formula :

25



(in which R^5 is lower alkyl or
 ar(lower)alkyl
 which may have suitable
 substituent(s), and

30

35

- 99 -

X^1 is an acid residue),

Y is CH or N and

Z is CH or N,

with proviso that

5 when R^3 is pyridyl; piperidyl which may have hydroxy group; piperazinyl which has lower alkyl group or hydroxy(lower)alkyl group; morpholinyl; lower alkenylamino; hydroxy(lower)alkylamino; phenylamino which may have lower alkoxy group or halogen on the benzene ring; halophenyl(lower)-alkylamino; phenylsulfonylamino which has nitro group, amino group or halogen on the benzene ring; or

10 amino substituted with two substituents selected from the group consisting of lower alkyl and hydroxy(lower)alkyl, and

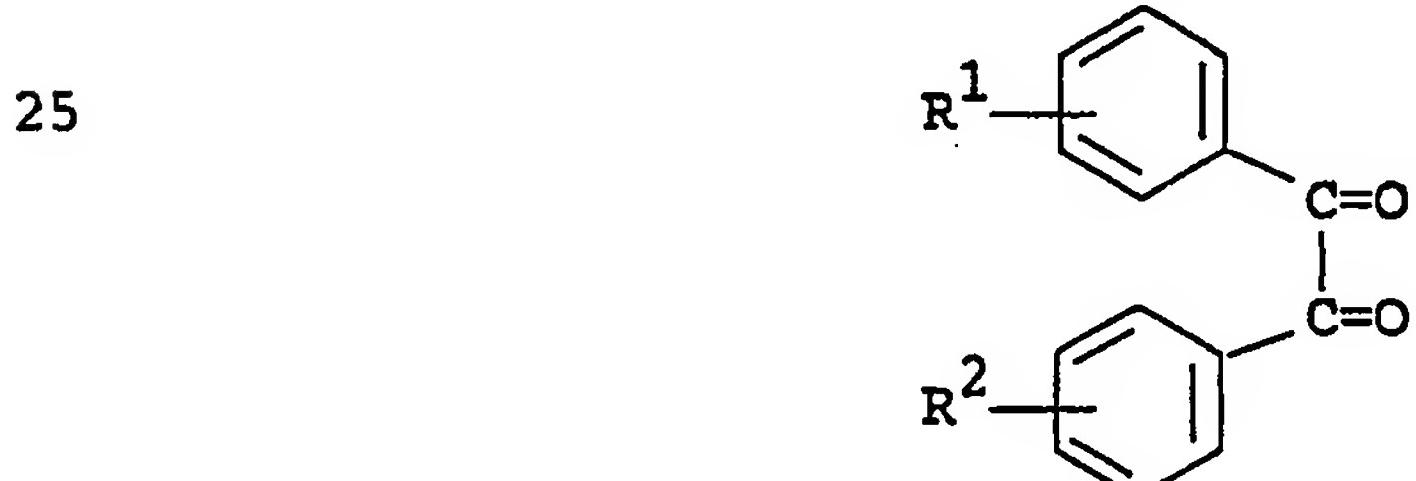
Y is N,

then Z is CH,

20 or a salt thereof,

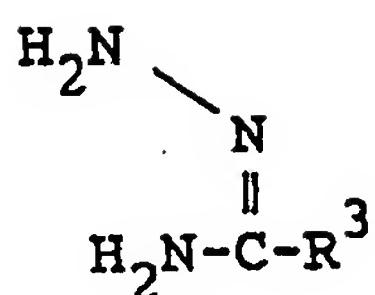
which comprises

(1) reacting a compound of the formula :

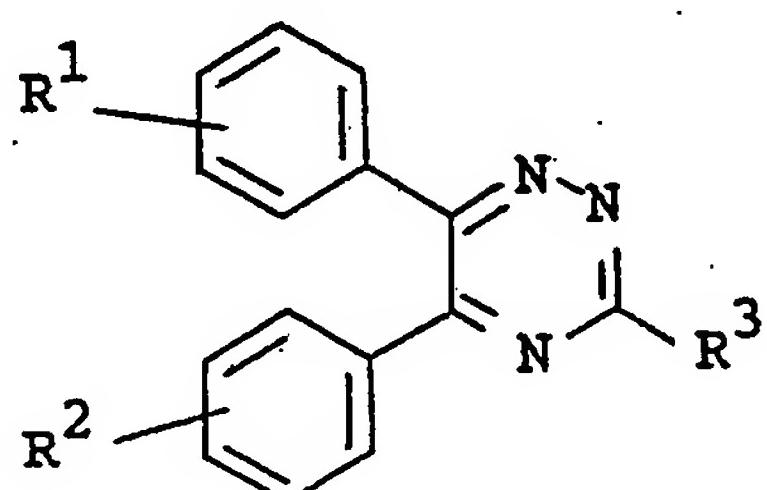


30 wherein R^1 and R^2 are each as defined above,
with a compound of the formula :

- 100 -

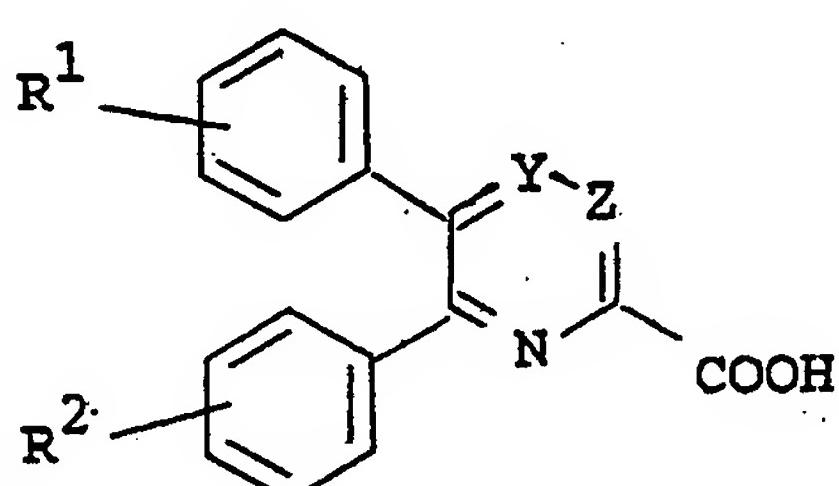


5 wherein R^3 is as defined above,
or a salt thereof to give a compound of the formula :



10 15 wherein R^1 , R^2 and R^3 are each as defined above,
or a salt thereof, or

(2) reacting a compound of the formula :



20 25 wherein R^1 , R^2 , Y and Z are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof with a compound of the formula :

30

wherein $-\text{N}(\text{H}-\text{N})-$ is mono(or di)lower alkylamino,

35

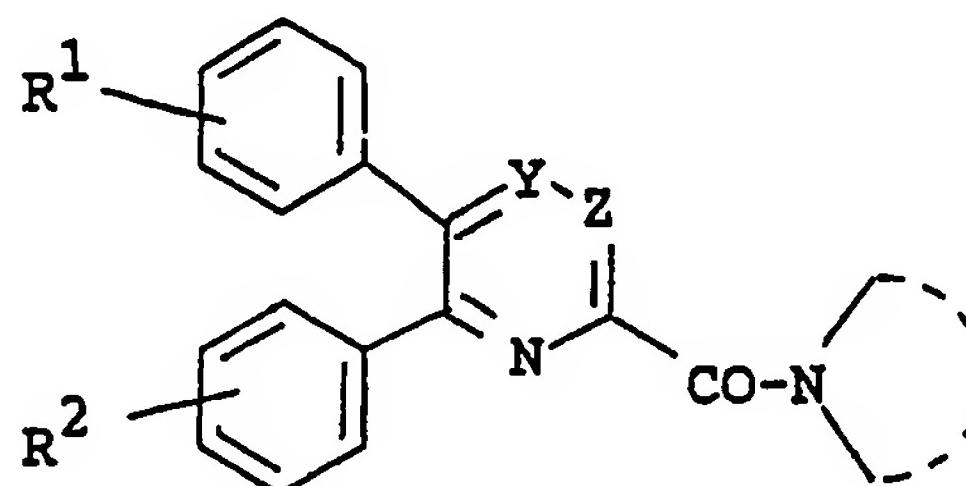
di(lower)alkylamino-(lower)alkylamino,
heterocyclicamino which may have
suitable substituent(s), or

- 101 -

heterocyclic group containing at least one nitrogen atom which may have suitable substituent(s),
or a salt thereof to give a compound of the formula :

5

10

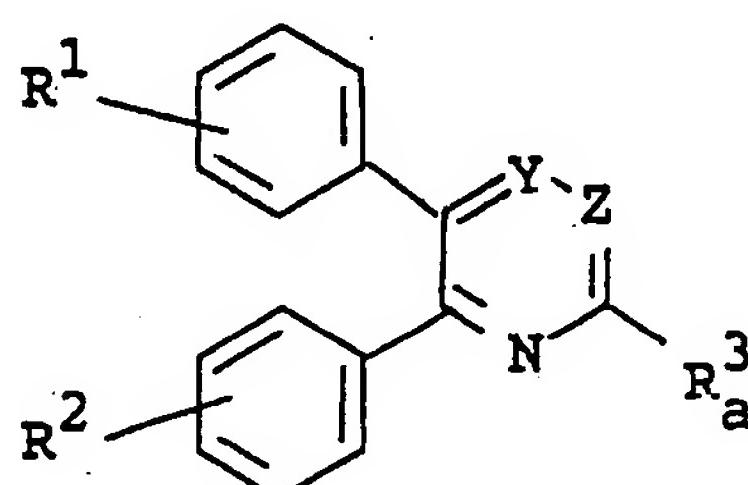


15

wherein R¹, R², Y, Z and -N- are each as defined above,
or a salt thereof, or

(3) subjecting a compound of the formula :

20

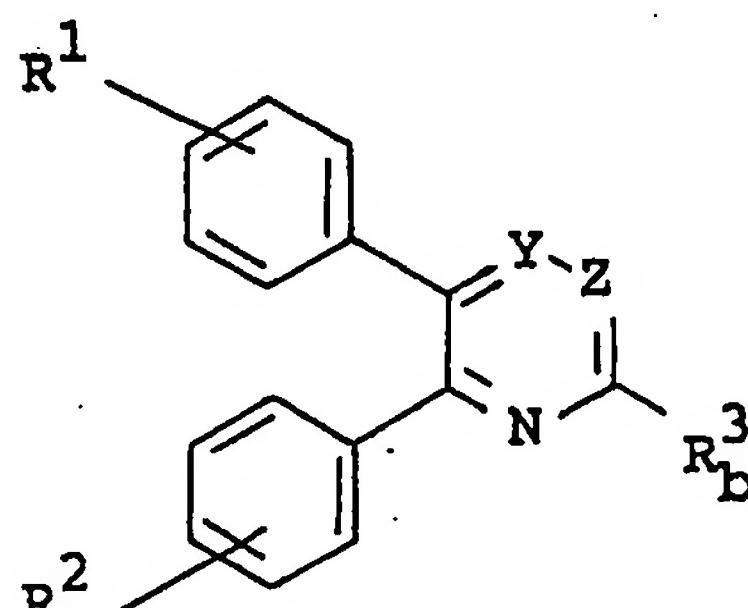


25

wherein R¹, R², Y and Z are each as defined above and
R³a is protected amino(lower)alkyl,
or a salt thereof to elimination reaction of the
amino-protective group to give a compound of the
formula :

30

35



- 102 -

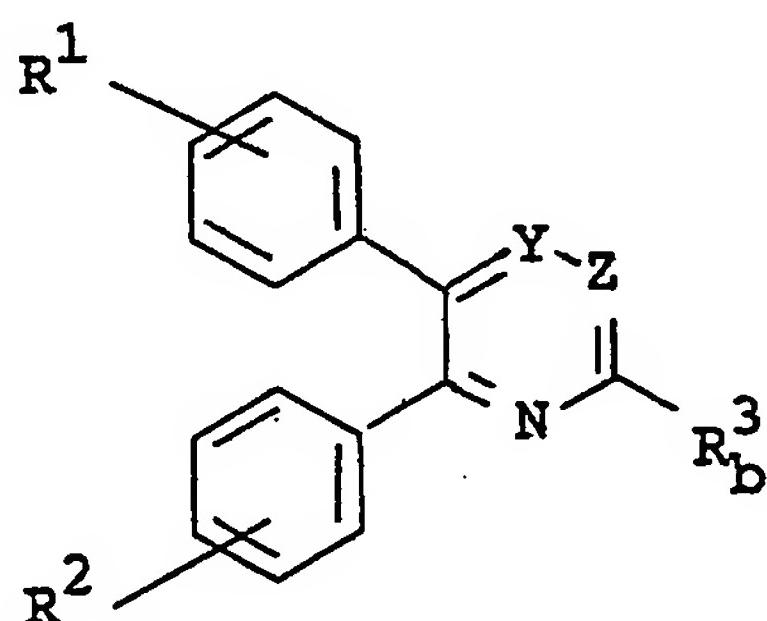
wherein R^1 , R^2 , Y and Z are each as defined
above and

R_b^3 is amino(lower)alkyl,
or a salt thereof,

5 or

(4) subjecting a compound of the formula :

10

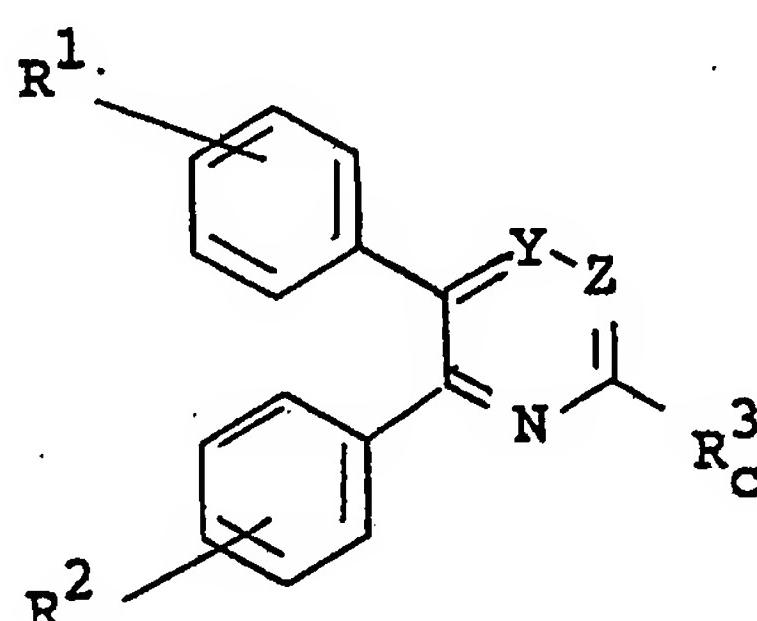


15

wherein R^1 , R^2 , R_b^3 , Y and Z are each as defined
above,

20 or its reactive derivative at the amino group
or a salt thereof to acylation reaction to give
a compound of the formula :

25



30

wherein R^1 , R^2 , Y and Z are each as defined above and
 R_c^3 is acylamino(lower)alkyl,

or a salt thereof,

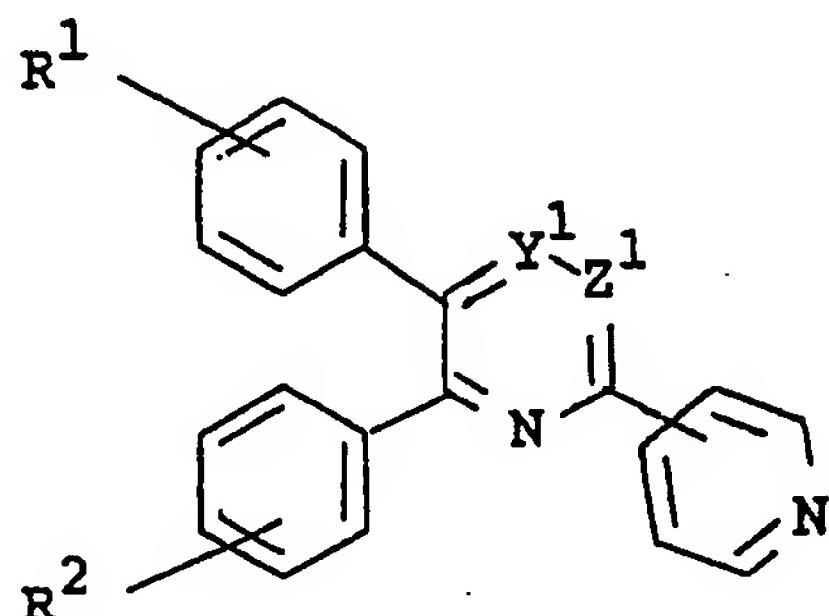
or

35

- 103 -

(5) reacting a compound of the formula :

5



10

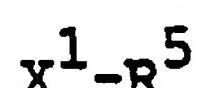
wherein R¹ and R² are each as defined above,

y¹ is CH or N and

z¹ is CH or N,

or a salt thereof with a compound of the formula :

15

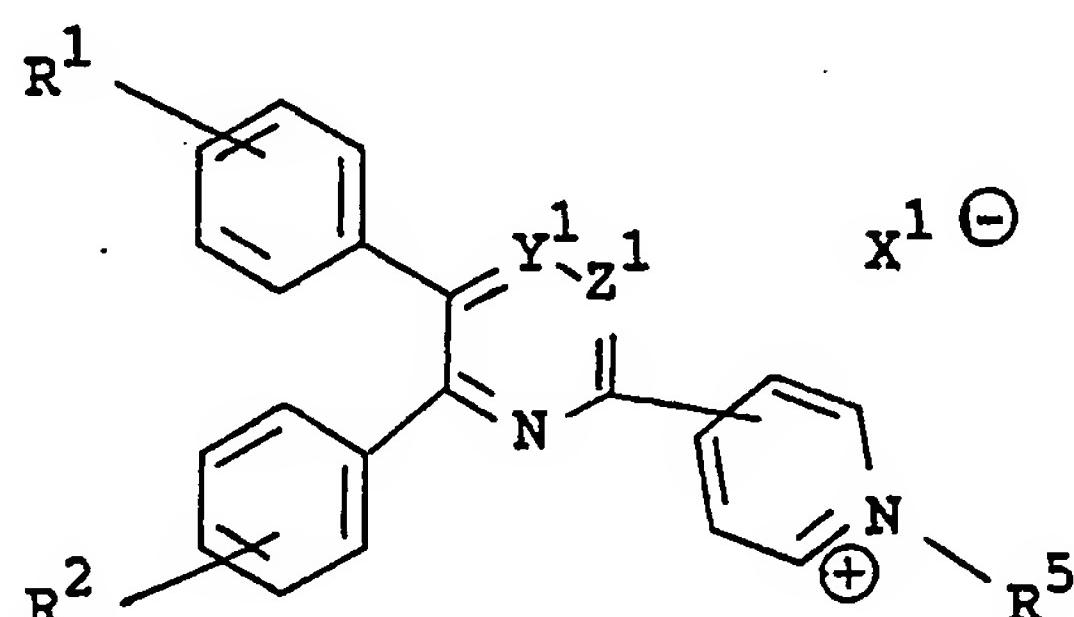


wherein R⁵ and X¹ are each as defined above,

to give a compound of the formula :

20

25



30

wherein R¹, R², R⁵, Y¹, Z¹ and X¹ are each as defined above,

or a salt thereof,

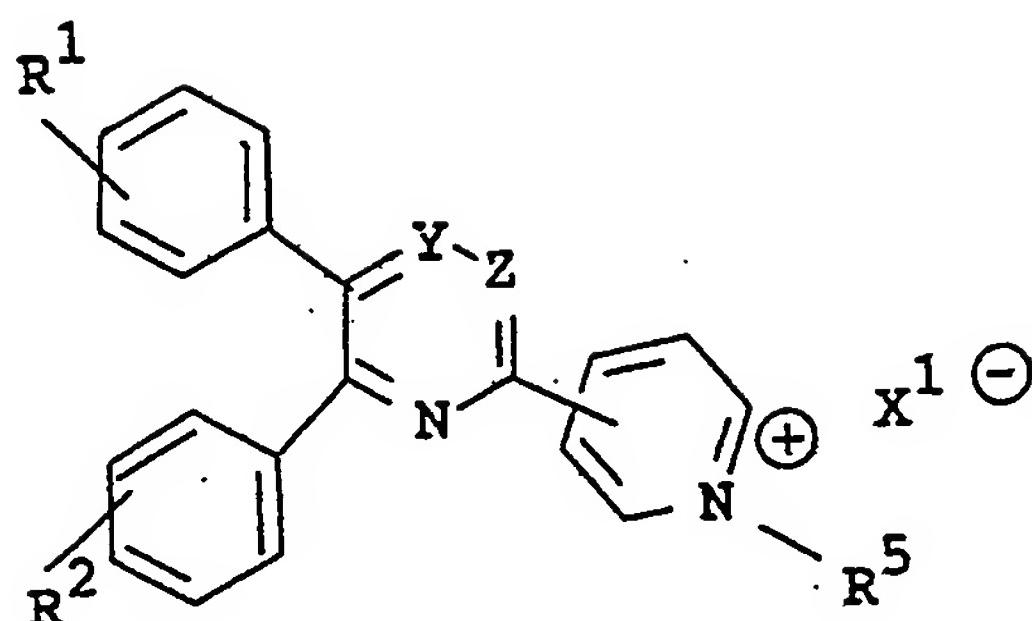
or

(6) subjecting a compound of the formula :

35

- 104 -

5



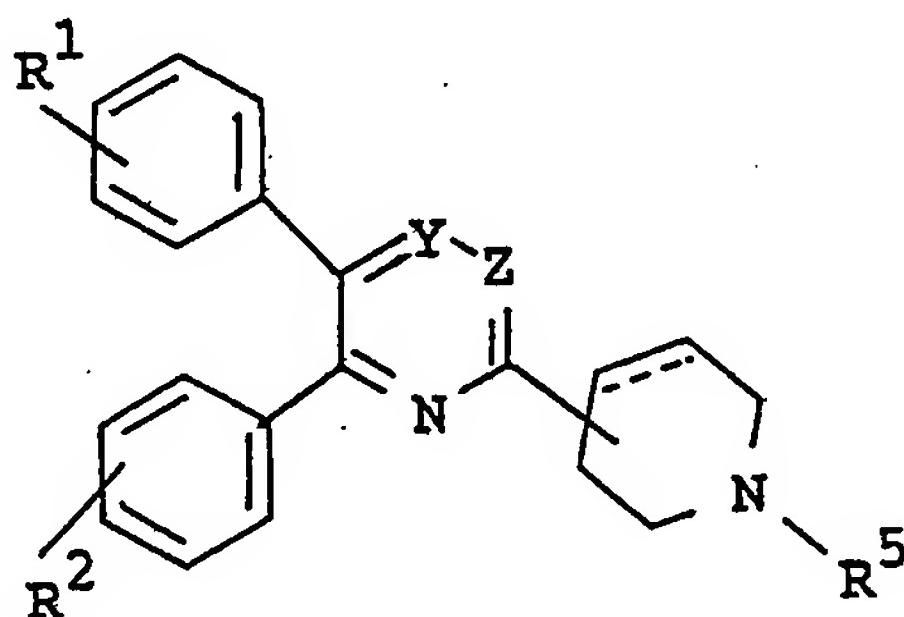
10

wherein R¹, R², R⁵, Y, Z and X¹ are each as defined above,

20

or a salt thereof to reduction reaction to give a compound of the formula :

15



25

wherein R¹, R², R⁵, Y and Z are each as defined above and

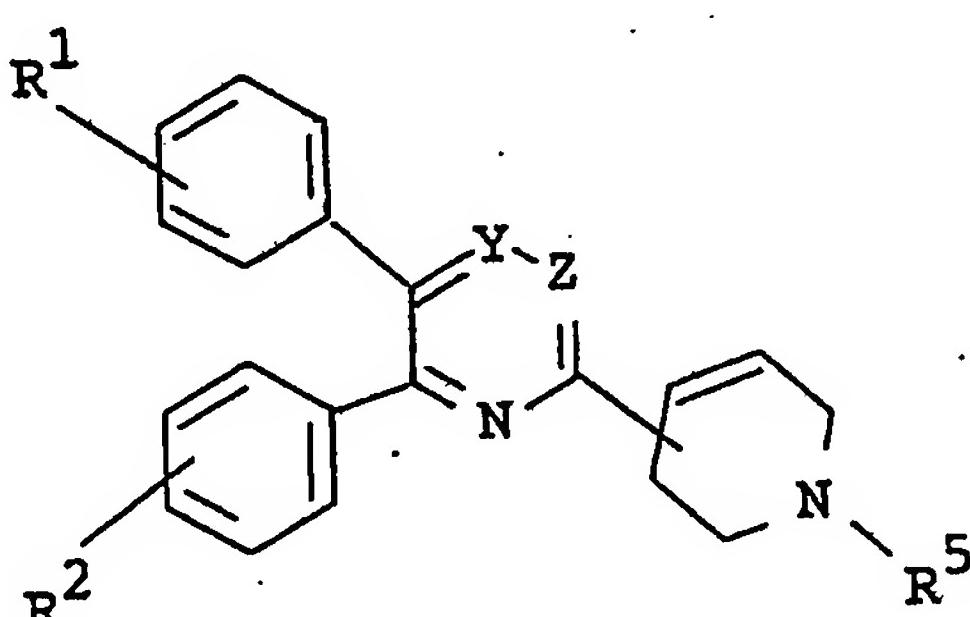
— means a single or double bond,

25

or a salt thereof, or

(7) subjecting a compound of the formula :

30



35

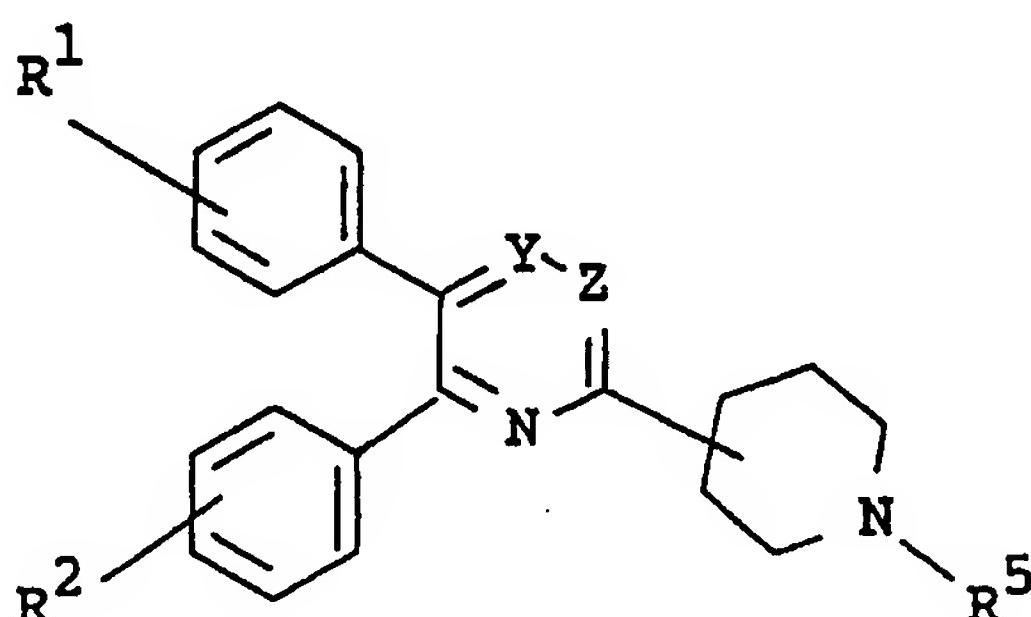
- 105 -

wherein R^1 , R^2 , R^5 , Y and Z are each as defined above,

or a salt thereof to reduction reaction to give a compound of the formula :

5

10



15

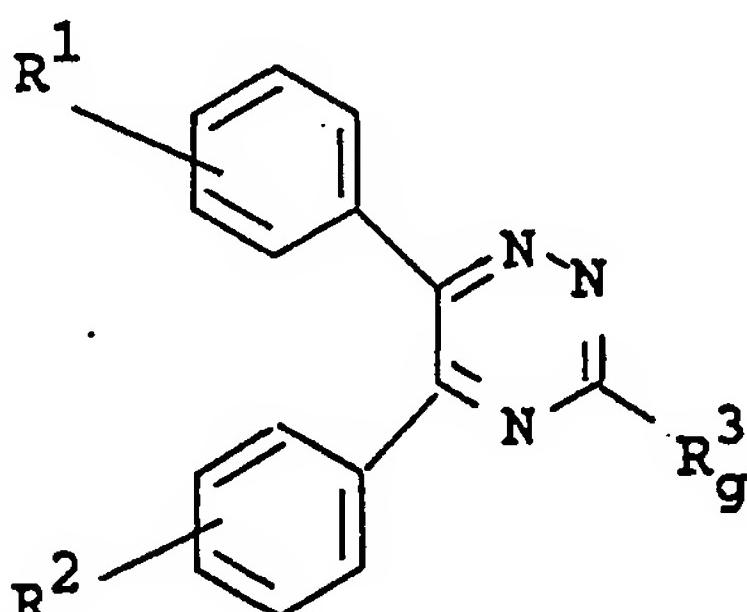
wherein R^1 , R^2 , R^5 , Y and Z are each as defined above,

or a salt thereof, or

(8) reacting a compound of the formula :

20

25



30

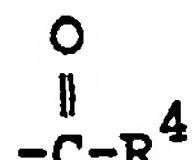
35

wherein R^1 and R^2 are each as defined above and R_g^3 is heterocyclic group selected from the group consisting of pyridyl, tetrahydropyridyl, piperidyl, piperazinyl and morpholinyl, which may have suitable substituent(s); substituted amino; carboxy(lower)alkenyl;

- 106 -

carboxy(lower)alkyl;
 hydroxy(lower)alkyl; amino(lower)alkyl
 which may have suitable substituent(s);
 a group of the formula :

5



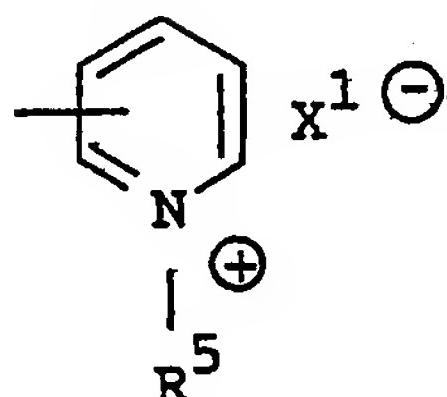
10

(in which R^4 is hydrogen, ethoxy,
 mono(or di)lower
 alkylamino,
 di(lower)alkylamino(lower)-
 alkylamino,
 heterocyclicamino which
 may have suitable
 substituent(s), or
 heterocyclic group which
 may have suitable
 substituent(s));

15

or a group of the formula :

25

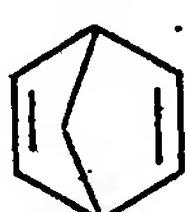


30

(in which R^5 is lower alkyl or
 ar(lower)alkyl which may
 have suitable
 substituent(s), and
 X^1 is an acid residue),

or a salt thereof with a compound of the formula :

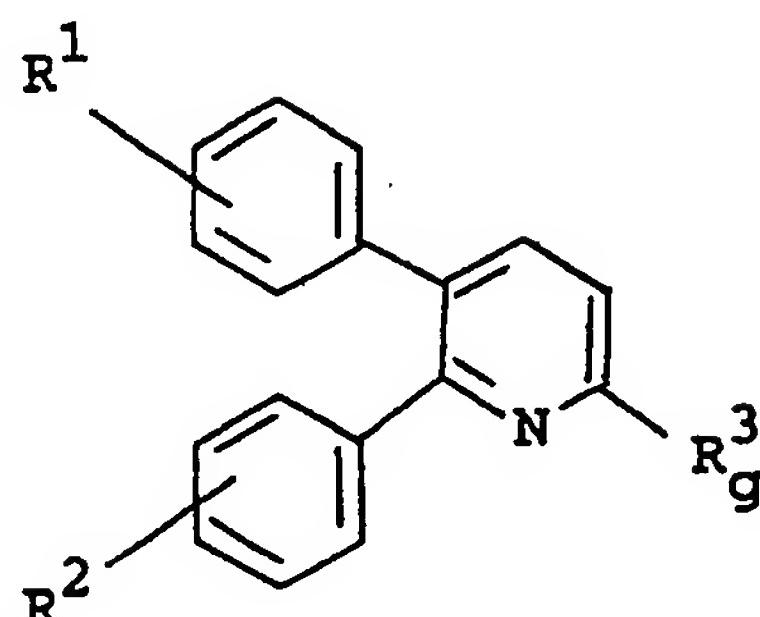
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- 107 -

to give a compound of the formula :

5

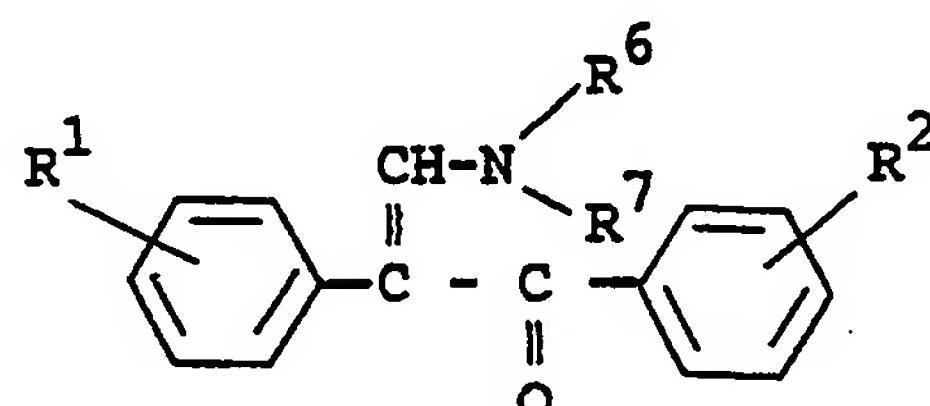


10

wherein R¹, R² and Rg³ are each as defined above,
or a salt thereof, or

(9) reacting a compound of the formula :

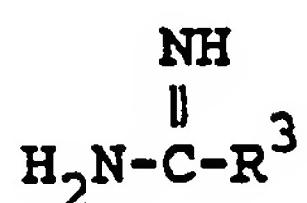
15



20

wherein R¹ and R² are each as defined above, and
R⁶ and R⁷ are each lower alkyl,
or a salt thereof with a compound of the formula :

25



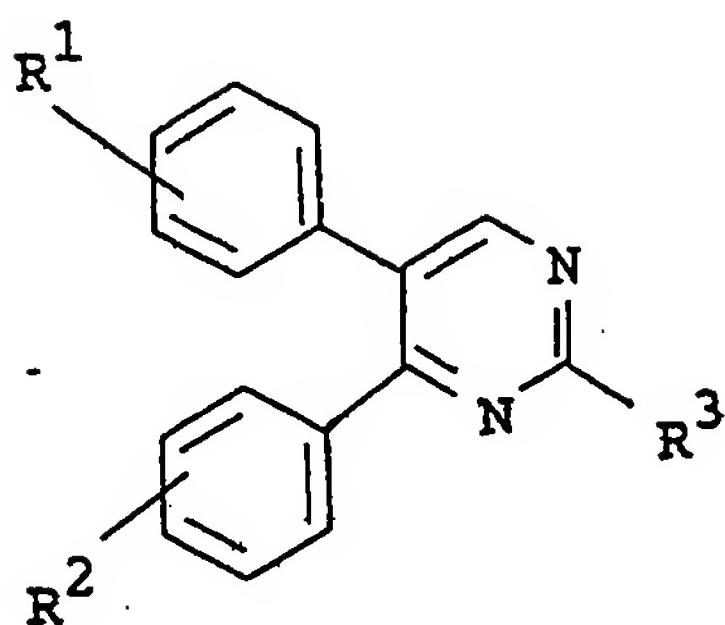
30

wherein R³ is as defined above,
or a salt thereof to give a compound of the formula :

35

- 108 -

5



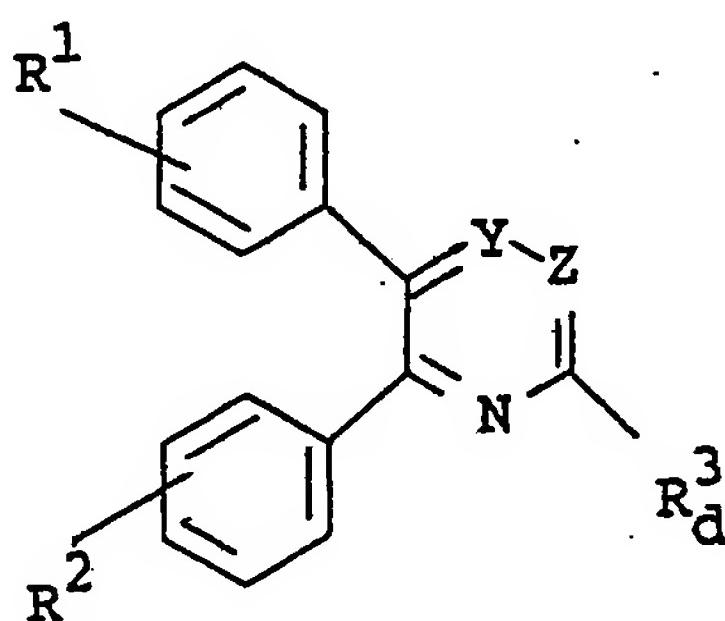
10

wherein R^1 , R^2 and R^3 are each as defined above,
or a salt thereof, or

20

(10) subjecting a compound of the formula :

15

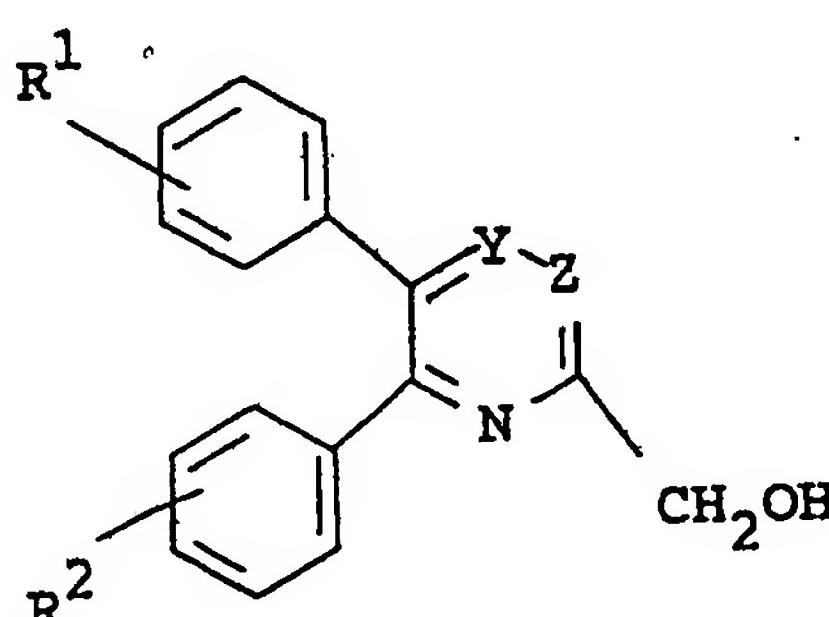


20

25

wherein R^1 , R^2 , Y and Z are each as defined above and
 R^3_d is carboxy or protected carboxy,
or a salt thereof to reduction reaction to give a
compound of the formula :

30



35

wherein R^1 , R^2 , Y and Z are each as defined above,

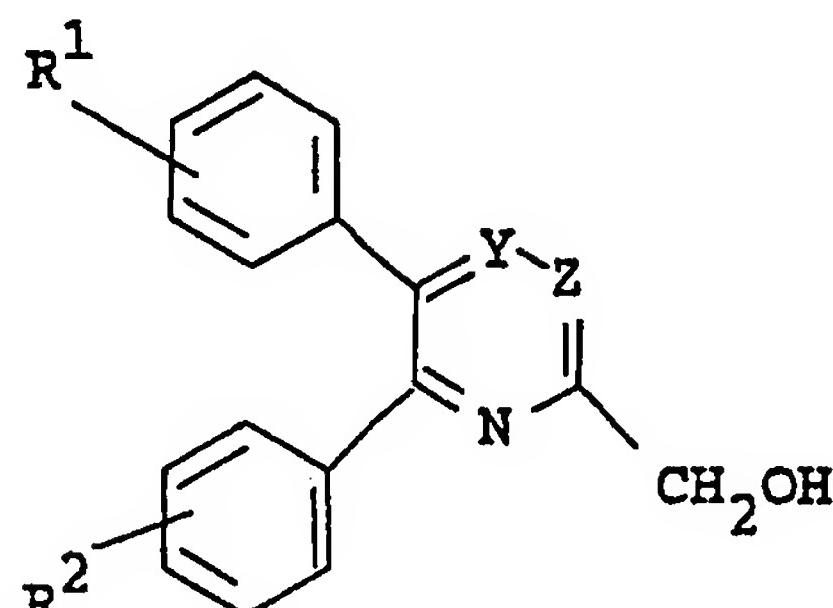
- 109 -

or a salt thereof, or

(11) subjecting a compound of the formula :

5

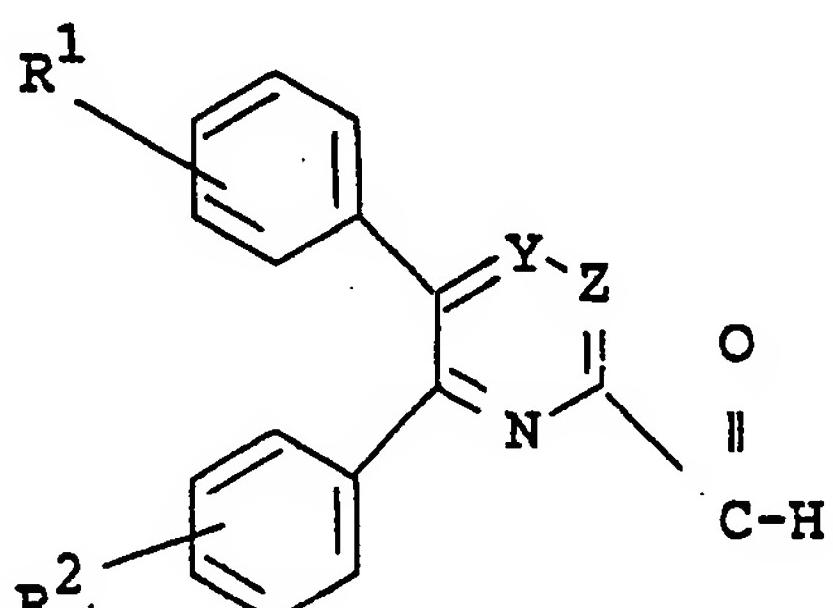
10



15

wherein R¹, R², Y and Z are each as defined above,
or a salt thereof to oxidation reaction to give
a compound of the formula :

20



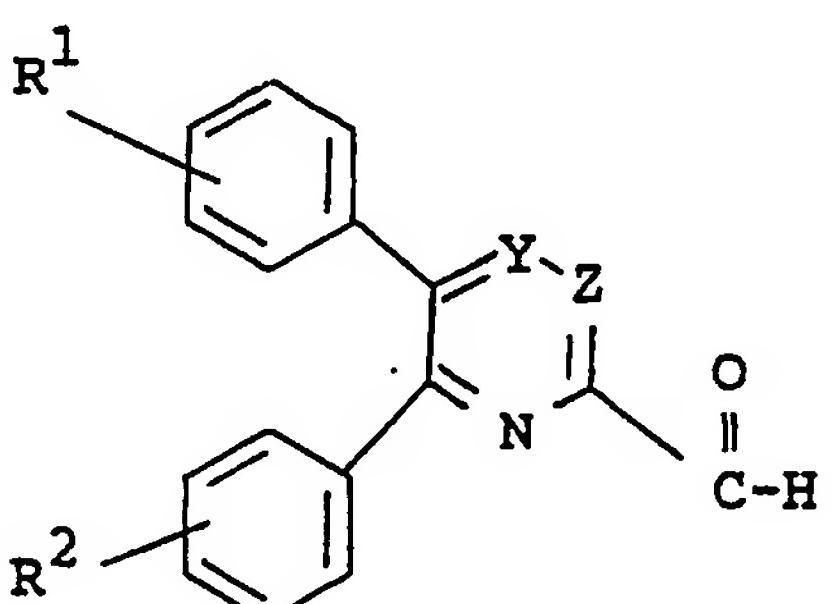
25

wherein R¹, R², Y and Z are each as defined above,
or a salt thereof, or

(12) reacting a compound of the formula :

30

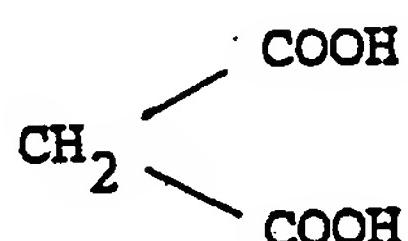
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- 110 -

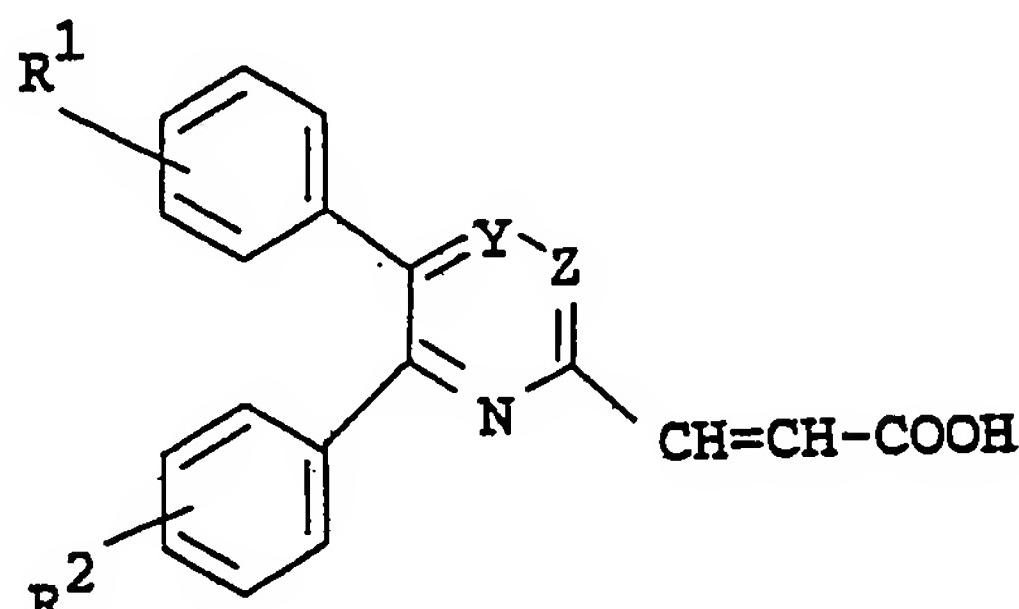
wherein R¹, R², Y and Z are each as defined above,
or a salt thereof with a compound of the formula :

5



10

15

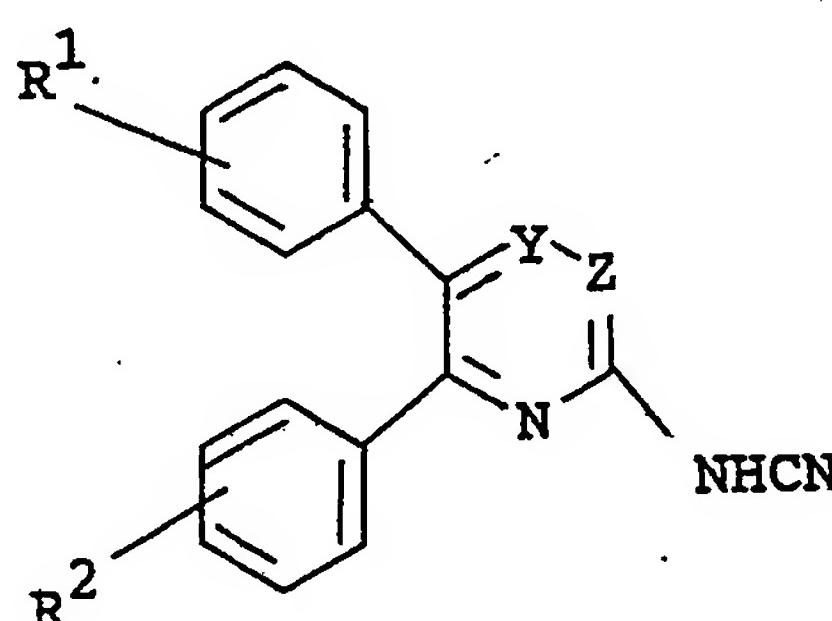


wherein R¹, R², Y and Z are each as defined above,
or a salt thereof, or

20

(13) reacting a compound of the formula :

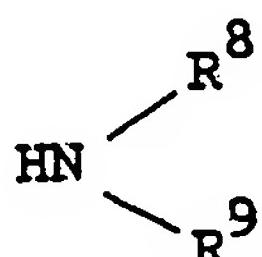
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30

wherein R¹, R², Y and Z are each as defined above,
or a salt thereof with a compound of the formula :

35



- 111 -

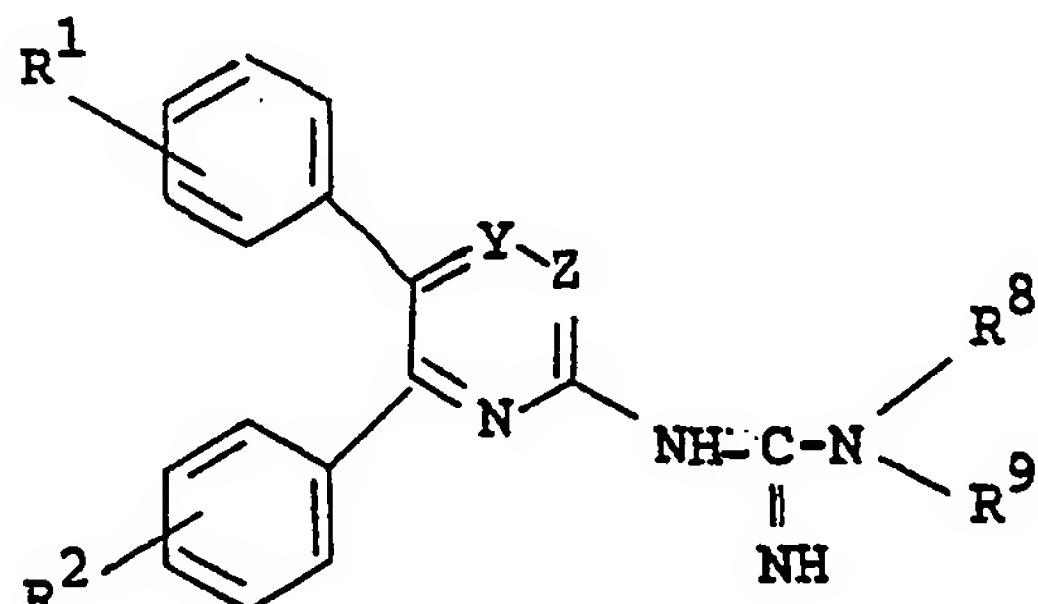
wherein R⁸ and R⁹ are each hydrogen, lower alkyl,
cyclo(lower)alkyl, ar(lower)alkyl,
heterocyclic group which may have
suitable substituent(s), or

5 R⁸ and R⁹ are linked together with the
attached nitrogen atom to form
heterocyclic group which may have
suitable substituent(s),

or a salt thereof to give a compound of the formula :

10

15



wherein R¹, R², R⁸, R⁹, Y and Z are each as defined
above,

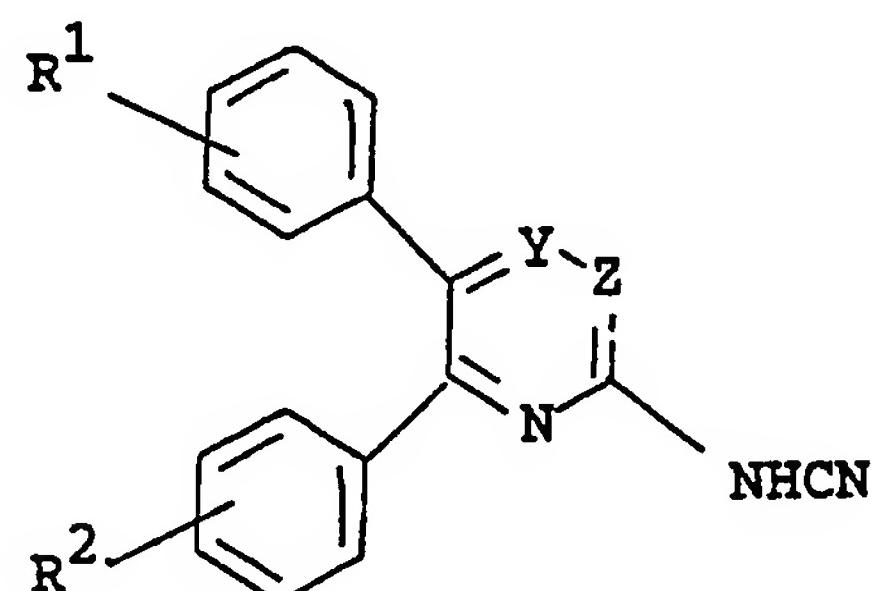
20

or a salt thereof, or

(14) reacting a compound of the formula :

25

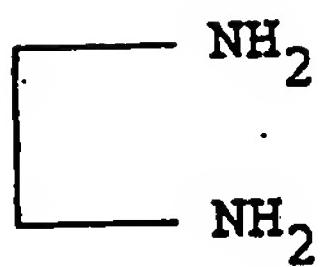
30



wherein R¹, R², Y and Z are each as defined above,
or a salt thereof with a compound of the formula :

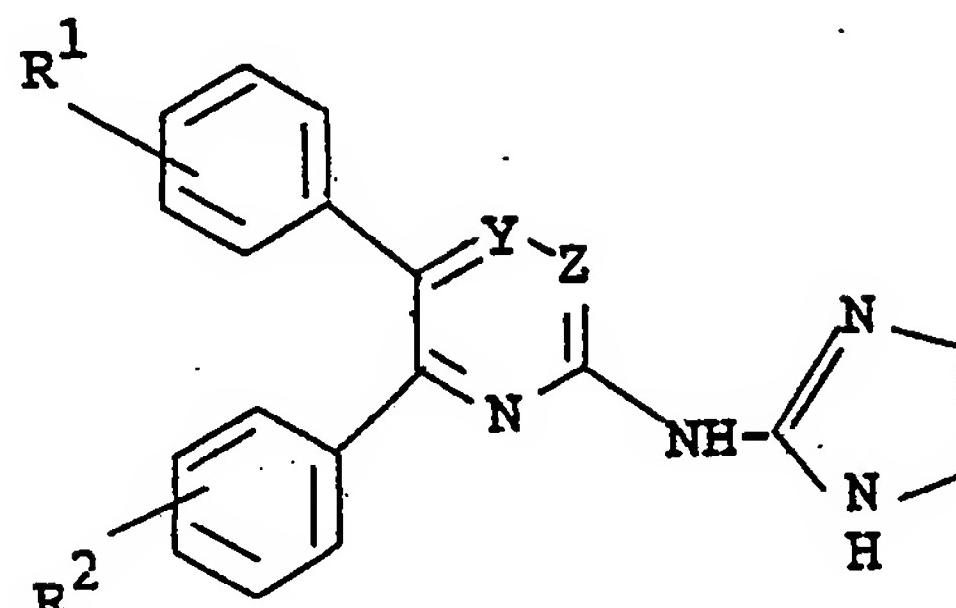
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- 112 -



5 or a salt thereof to give a compound of the formula :

10

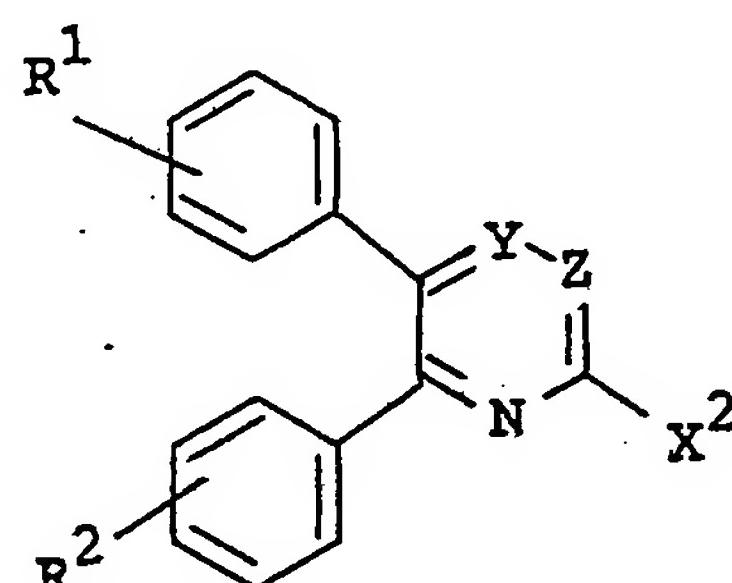


15

wherein R^1 , R^2 , Y and Z are each as defined above,
or a salt thereof, or

(15) reacting a compound of the formula :

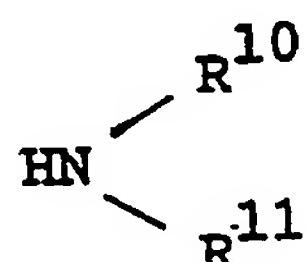
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25

wherein R^1 , R^2 , Y and Z are each as defined above and
 X^2 is a leaving group,
or a salt thereof with a compound of the formula :

30

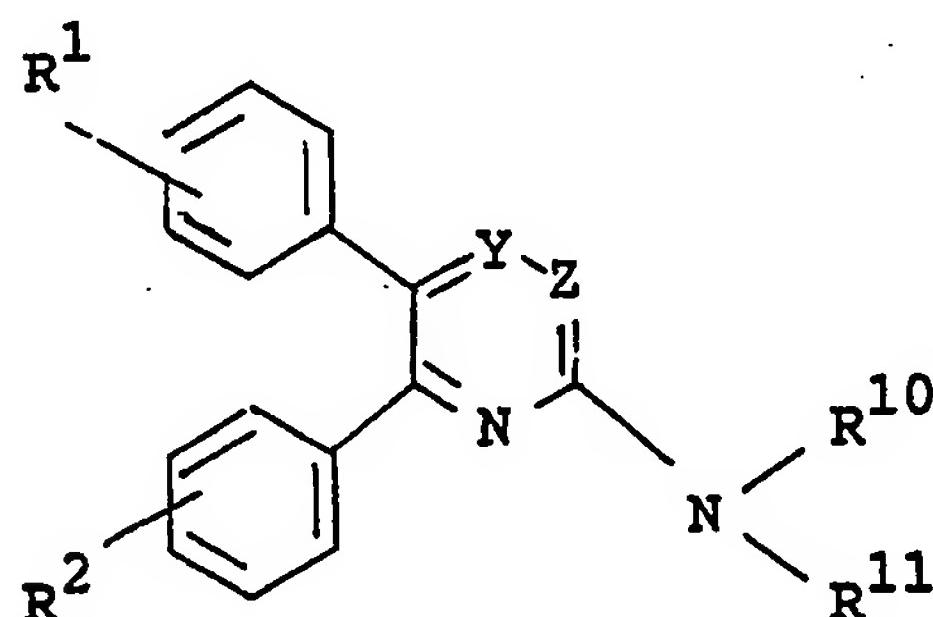


35

- 113 -

wherein R^{10} is hydrogen or lower alkyl and
 R^{11} is lower alkyl or 1-amino-1-iminomethyl,
or
 R^{10} and R^{11} are linked together with the
5 attached nitrogen atom to form
heterocyclic group which may have
suitable substituent(s),
or a salt thereof to give a compound of the formula :

10



15

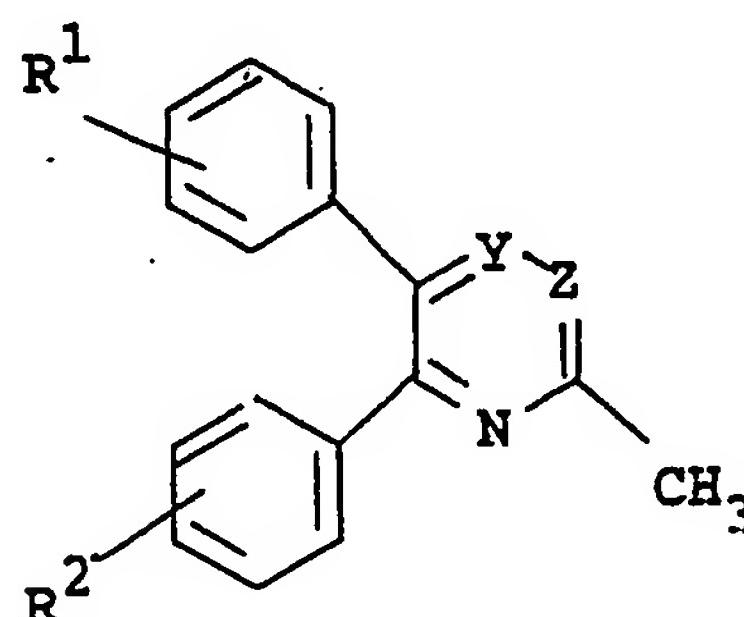
wherein R^1 , R^2 , R^{10} , R^{11} , Y and Z are each as defined
above,

20

or a salt thereof, or

(16) reacting a compound of the formula :

25



30

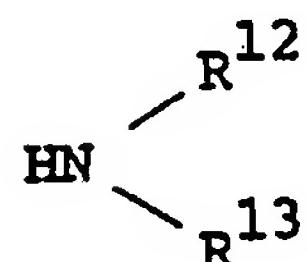
wherein R^1 , R^2 , Y and Z are each as defined above,
or a salt thereof with a compound of the formula :

35

HCHO

- 114 -

and a compound of the formula :

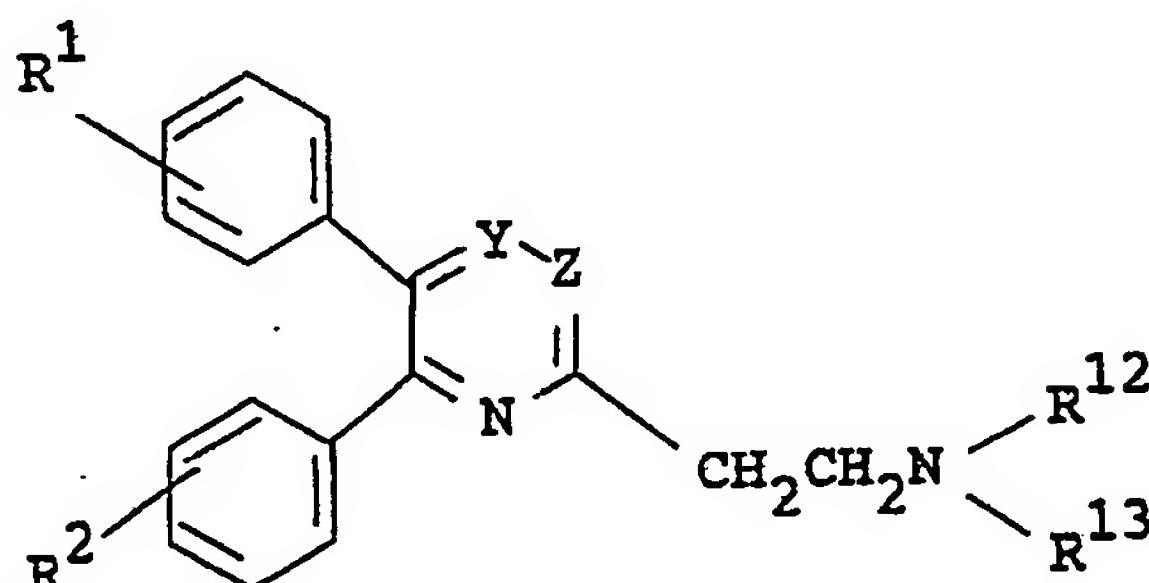


5

wherein R^{12} and R^{13} are each lower alkyl,
or a salt thereof to give a compound of the formula :

10

15



20

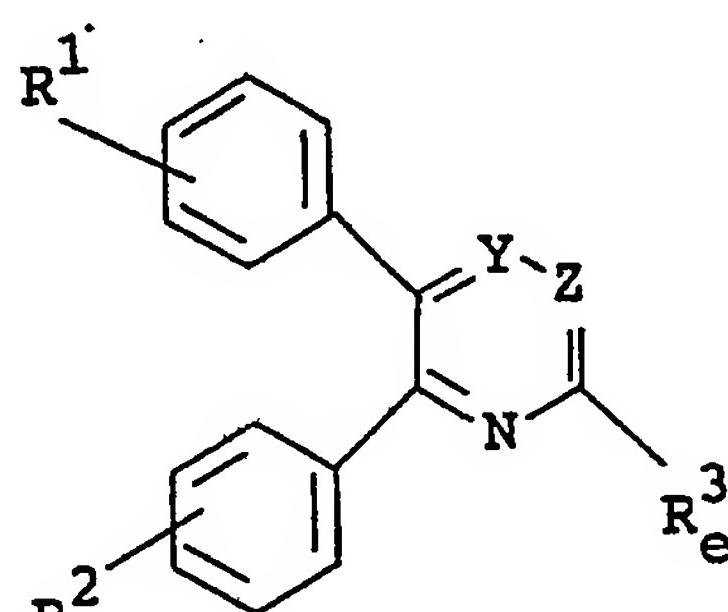
wherein R^1 , R^2 , R^{12} , R^{13} , Y and Z are each as defined
above,

or a salt thereof, or

(17) subjecting a compound of the formula :

25

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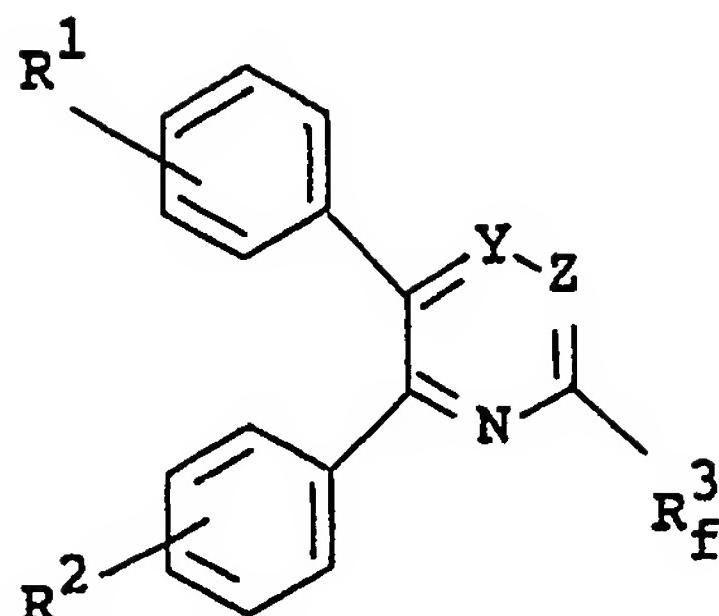


35

wherein R^1 , R^2 , Y and Z are each as defined above and
 R_e^3 is carboxy(lower)alkenyl,
or a salt thereof to reduction reaction to give
a compound of the formula :

- 115 -

5

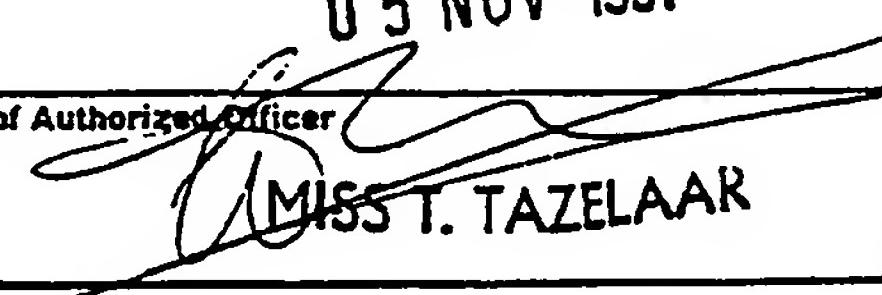


wherein R¹, R², Y and Z are each as defined above and
10 R³_f is carboxy(lower)alkyl,
or a salt thereof.

- 10. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
- 15. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as antithrombotic, vasodilating or anti-inflammatory agent.
- 20. A method for the prophylactic or therapeutic treatment of thrombosis, hypertension, cardiovascular or cerebrovascular diseases, or inflammation which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.
- 25. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 91/01042

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁵		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 253/065, 07, 403/04, 06, 12, 213/44, 54, 241/12, 20, 239/26, 42, 401/04, 06, 12, 413/04, 06, 12, A 61 K 31/395		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	C 07 D; A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US, A, 3979516 (W.B. LACEFIELD) 7 September 1976, see the whole document	1-4, 6, 9- 10, 13 5, 7, 8
A	---	
X	US, A, 4021553 (W.B. LACEFIELD ET AL.) 3 May 1977, see the whole document	1-4, 9- 10, 13 5-8
A	---	
X	US, A, 4318911 (W.B. LACEFIELD) 9 March 1982, see the whole document	1-4, 9- 10, 13 5-8
A	---	
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
3rd October 1991	05 NOV 1991	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer  MISS T. TAZELAAR	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	WO, A1, 8904308 (TERUMO KABUSHIKI KAISHA) 18 May 1989, see examples 14-15 and table 1	1-4, 9- 10, 13
A	--	5-8
X	Chemical Abstracts, volume 104, no. 1, 6 January 1986, (Columbus, Ohio, US), Pitet G. et al.: "Synthesis and pharmacological profile of new diaryl-as-triazines", see page 18, abstract 228W, & Bull. Chim. Farm. 1985, 124(6), 271- 278	1-4, 9- 10, 13
A	--	5-8
X	FR, A, 2173868 (MCNEIL LABORATORIES, INCORPORATED) 12 October 1973, see examples 41-45, pages 32-33 and claim 14	1-4, 9- 10, 13
A	--	5-8
A	EP, A2, 0088593 (ELI LILLY AND COMPANY) 24 September 1983, see pages 1-2	1-10, 13

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹**

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers 11-12, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,
see rule 39.

2. Claim numbers 1-3, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out. Specifically:

The scope of claims 1-3 is so broadly formulated that a very wide range of structures are included. These claims have thus not been fully searched.

3. Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/JP 91/01042

SA 34780

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 30/08/91.
The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 3979516	07/09/76	US-A-	3948894	06/04/76
		US-A-	3989831	02/11/76
		US-A-	4013654	22/03/77
		US-A-	4008232	15/02/77
US-A- 4021553	03/05/77	NONE		
US-A- 4318911	09/03/82	NONE		
WO-A1- 8904308	18/05/89	EP-A-	0397859	22/11/90
		JP-A-	1128971	22/05/89
		JP-A-	1128972	22/05/89
		JP-A-	1135775	29/05/89
FR-A- 2173868	12/10/73	NONE		
EP-A2- 0088593	24/09/83	AU-B-	547581	24/10/85
		AU-D-	1202983	08/09/83
		CA-A-	1195327	15/10/85
		GB-A-B-	2116179	21/09/83
		JP-A-	58162582	27/09/83
		US-A-	4513135	23/04/85
		US-A-	4585861	29/04/86

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82